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Health and Environmental Effects Profile for Nitrobenzene

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR NITROBENZENE

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
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16. ABSTRACT

The Health and Environmental Effects Profile for nitrobenzene was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA) and to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Nitrobenzene has been determined to be a systemic toxicant. An Acceptable Daily Intake (ADI), defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect, for nitrobenzene is 0.032 mg/day for inhalation exposure.

The Reportable Quantity (RQ) value of 1, 10, 100, 1000 or 5000 pounds is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified by CERCLA based on chronic toxicity. The RQ value for nitrobenzene is 100.

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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste and Emergency Response by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA), as well as to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched." The literature search material is current through November, 1984.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor of q_1^* (U.S. EPA, 1980) is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

Reportable quantities (RQs) based on both chronic toxicity and carcinogenicity are derived. The RQ is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified under CERCLA. These two RQs (chronic toxicity and carcinogenicity) represent two of six scores developed (the remaining four reflect ignitability, reactivity, aquatic toxicity and acute mammalian toxicity).

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA and CERCLA dockets.

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LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
BCF	Bioconcentration factor
BOD	Biological oxygen demand
CAS	Chemical Abstract Service
CNS	Central nervous system
COD	Chemical oxygen demand
DNA	Deoxyribonucleic acid
EC_{50}	Median effective concentration
K_{oc}	Soil sorption coefficient standardized with respect to organic carbon
K_{ow}	Octanol/water partition coefficient
LC_{50}	Concentration lethal to 50% of recipients
LD_{50}	Dose lethal to 50% of recipients
NOEC	No-observed-effect concentration
po	Per os
ppb	Parts per billion
ppm	Parts per million
RQ	Reportable quantity
STEL	Short-term exposed level
TLV	Threshold limit value
TWA	Time-weighted average
UV	Ultraviolet
WS	Water solubility

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

Nitrobenzene is the common chemical name for this compound which is also known by the synonyms nitrobenzol, oil of mirbane and NB. The structure, molecular weight, and empirical formula for nitrobenzene are as follows:

Molecular weight: 123.06

Empirical formula: $C_6H_5NO_2$

The CAS Registry number for this compound is 98-95-3.

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Nitrobenzene is a liquid with a bitter almond odor (Dunlap, 1981); its color varies from pale yellow to a yellowish-brown, depending on the purity. It is readily soluble in most organic solvents and is a good solvent for many organic compounds. Selected physical properties are listed below:

Melting point:	5.85°C	Dunlap, 1981
Boiling point (760 mm Hg):	210.9°C	Dunlap, 1981
Specific gravity:	1.199(24/4°C)	Dunlap, 1981
Refractive index:	1.553(20°C)	Dunlap, 1981
Vapor density (air=1):	4.1	Dunlap, 1981
Flash point (closed cup):	88°C	Dunlap, 1981
Water solubility: at 20°C at 25°C	 1900 ppm 2090 ppm	 Verschueren, 1983 Banerjee et al., 1980
Henry's Law Constant	2.3×10^{-5} atm-m³/md (25°C)	Hine and Mookerjee (1975)
	1.3×10^{-5} atm-m³/mol (20°C)	Mabey et al. (1981)

Vapor pressure, mmHg:		
at 20°C	0.15	Verschueren, 1983
at 30°C	0.35	Verschueren, 1983
at 25°C	0.27	Neely, 1976
Log K_{ow}:	1.88	Hansch and Leo, 1979
	1.83	Banerjee et al., 1980
	1.84	Geyer et al., 1984
Conversion factor (air):	1 ppm = 5.12 mg/m³	Verschueren, 1983

Nitrobenzene can undergo halogenation, sulfonation, and nitration but it does not undergo Friedel-Crafts reactions (Dunlap, 1981). The reduction of the nitro group to yield aniline is the most commercially important reaction of nitrobenzene.

1.3. PRODUCTION DATA

The current U.S. manufacturers of nitrobenzene are as follows (CMR, 1984; SRI, 1984):

Manufacturer	Annual Capacity (10^6 lbs)
DuPont (Beaumont, TX)	350
DuPont (Gibbstown, NJ)	340
First Mississippi Corp. (Pascagoula, MS)	335
Mobay (New Martinsville, WV)	200
Rubican Chem. (Geismar, LA)	375

Domestic production of nitrobenzene in 1981, 1982, and 1983 has been reported to be 901.6, 774.8 and 840.7 million pounds, respectively (USITC, 1982, 1983, 1984).

Nitrobenzene is manufactured commercially by directly nitrating benzene with a mixture of nitric and sulfuric acids (Dunlap, 1981).

1.4. USE DATA

About 97.5% of all nitrobenzene produced is used in the synthesis of aniline (CMR, 1984). The remaining 2.5% is used in the synthesis of N-acetyl p-aminophenol (an analgesic similar to Tylenol®) and other chemicals, as a solvent and in the refining of certain lubricating oils (CMR, 1984; Dunlap,1981). Nitrobenzene has been listed as an ingredient in cleaners for wood products, veterinary liniments (U.S. EPA, 1977), and metal and shoe polishes (Hawley, 1977).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

Like other chemicals, the fate of nitrobenzene in the environment depends upon the ability of the compound to undergo chemical, photochemical, and biological reactions and to transport or partition from one environmental matrix into another. The individual fate processes are discussed below.

2.1. WATER

2.1.1. Hydrolysis. Experimental data were not located in literature cited in the appendix; however, Mabey et al. (1981) and Callahan et al. (1979) reported that hydrolysis of nitrobenzene in aquatic media is not expected to be significant.

2.1.2. Oxidation. Chemical oxidation of organic compounds in aquatic environments may occur due to several different oxidants which are primarily generated photochemically in water by sunlight (Mabey et al., 1981); these oxidants include the hydroxyl radical (•OH), peroxyl radical (RO_2•) and singlet oxygen. Estimated rate constants for reaction of nitrobenzene with RO_2• or singlet oxygen indicate that these reactions are not environmentally significant (Mabey et al., 1981).

Anbar and Neta (1967) reported that the rate constant for the reaction of nitrobenzene with •OH is 2×10^9 M^{-1} sec^{-1} at room temperature; assuming an average aquatic •OH concentration of 10^{-17} M, a half-life of 400 days is calculated. Dorfman and Adams (1973) reported the rate constant with •OH at 25°C to be 3.2×10^9 M^{-1} sec^{-1}, which yields a half-life of 250 days. The photooxidation of nitrobenzene solution in the presence of dilute H_2O_2 produced three nitrophenol isomers that have been identified as products of •OH reaction with nitrobenzene (Draper and Crosby, 1984).

2.1.3. Photolysis. The UV spectrum of nitrobenzene in a cyclohexane or light petroleum solvent displays an absorption maxima at ~256 nm, but additionally shows significant absorption in the environmentally significant range between 300 and 400 nm (Leermakers et al., 1966; Mabey et al., 1981); this indicates a potential for direct photolysis in the environment.

Zepp and Schlotzhauer (1983) measured the photolysis rate of nitrobenzene in distilled water and in water containing algae relative to the photolysis rate of p-nitroanisole. The laboratory procedure used to determine the photolysis rates involved exposing test solutions of the compounds to sunlight. A direct photolysis half-life (computed for average sunlight at 40°N latitude) of 6-17 hours, depending on the month of the year, was determined for p-nitroanisole. Relative to this rate, nitrobenzene was found to have a 10 times slower direct photolysis rate in distilled water. These rates of photolysis may be applicable to near surface conditions only in natural bodies of water; therefore, actual photolysis rates in the environment can be expected to require longer periods of time. The presence of algae did not accelerate the photolysis of nitrobenzene.

Barltrop and Bunce (1968) examined the photoly is of nitrobenzene (0.5 g/100 ml solvent) in various hydrogen abstractable organic solvents irradiated with light of wavelength >290 nm. Using irradiation times of 2-5 hours, degradation of nitrobenzene was observed to range from 25-97% depending on the solvent, with aniline being formed as a typical product. In the absence of hydrogen abstractable compound(s) in water, this reaction may not be important in natural water bodies.

With the exception of algae, the photosensitized photolysis of nitrobenzene in natural water has not been reported. Callahan et al. (1979) suggested that adsorption of nitrobenzene to humus matter in natural water may significantly increase the photolysis rate.

2.1.4. Microbial Degradation. Hallas and Alexander (1983) used a raw municipal sewage effluent to test the biodegradability of nitrobenzene under both aerobic and anaerobic conditions. Under aerobic conditions, 100% was degraded in 10 days after a 6-day lag period, while 50% was degraded under anaerobic conditions in 14 days after an 8-day lag period. Aniline was identified as a degradation product under anaerobic conditions. Using an anaerobic seed from a digester, Johnson and Young (1983) observed that nitrobenzene readily degrades under anaerobic conditions in serum bottle tests. Kobayashi and Rittman (1982) reported that nitrobenzene can be attacked by microbes from a waste stabilization pond.

Tabak et al. (1981) studied the biodegradability of 114 U.S. EPA priority pollutants to ascertain the extent of microbial degradation, and to determine the acclimation periods. Test methods involved static-culture flask-screening procedures using settled domestic wastewater as microbial inoculum. In case of nitrobenzene, 100% biodegradation was observed in 7 days with an original culture at an initial concentration of 5 ppm. The degradation was complete in 7 days with three subsequent subcultures. This classified nitrobenzene as significantly degradable with rapid adaptation.

Biodegradation of nitrobenzene in a bench-scale activated sludge reactor was determined to be significant with 94.5-97.0% removal, as measured by a 5-day BOD test (Stover and Kincannon, 1983; Kincannon et al., 1983). Davis et al. (1981) observed slight biodegradation of nitrobenzene in sewage sludge, with aniline and phenol as degradation products. In a model waste stabilization pond study, ~90% of nitrobenzene loss was accountable to degradation and only ~5% to volatilization (Davis et al., 1983). Pitter (1976) observed a 98.0% removal (based on COD) of nitrobenzene in a 20-day inoculation with an activated sludge. Chou et al. (1979) found nitrobenzene to be degradable in an anaerobic reactor.

In pure culture studies, McCormick et al. (1976) found that cell-free extracts of Veillonella alkalescens degrade nitrobenzene and Moore (1949) found that two species of Proactinomyces also degrade nitrobenzene.

In contrast to many of the above studies that indicate microbial degradability of nitrobenzene, a number of studies have found nitrobenzene to be either nondegradable or degradation-resistant in various activated sludges, wastewaters or cultures (Gomolka and Gomolka, 1983; Korte and Klein, 1982; Kawasaki, 1980; Sasaki, 1978; Kitano, 1978; Smith and Rosazza, 1974; Nei et al., 1973; Malaney and McKinney, 1966; Lutin et al., 1965; Marion and Malaney, 1964; Tabak et al., 1964; Chambers et al., 1963; Malaney, 1960; Heukelekian and Rand, 1955).

Biodegradation studies of nitrobenzene in natural water were not located in the available literature as cited in the Appendix.

2.1.5. Transport.

2.1.5.1. **VOLATILIZATION** -- Hine and Mookerjee (1975) experimentally measured the equilibrium water-to-air ratio of nitrobenzene in a dilute aqueous solution at 25°C to be 1047; the inverse of this value (9.6×10^{-4}) is the unitless Henry's Law Constant, which can be converted into a Henry's Law Constant of 2.3×10^{-5} atm-m³/mol. Mabey et al. (1981) used the solubility and vapor pressure of nitrobenzene at 20°C to calculate a Henry's Constant of 1.3×10^{-5} atm-m³/mol. Using solubility and vapor pressure data at 25°C (see Section 1.2.), a Henry's Constant of 2.1×10^{-5} atm-m³/mol can be calculated. These values of Henry's Constant suggest that volatilization of nitrobenzene from natural bodies of water is likely to be significant but not rapid (Lyman et al., 1982). From their study with laboratory-scale waste stabilization ponds, Davis et al. (1983) estimated the half-life of volatilization of nitrobenzene to be ~20 hours. Using the

Henry's Constant value of 2.3×10^{-5} atm-m³/mol, the following volatilization half-lives have been predicted using the U.S. EPA EXAMS computer simulation (Burns et al., 1981):

pond	22 days
river	12 days
oligotrophic lake	65 days
eutrophic lake	68 days

2.1.5.2. **ADSORPTION** -- Adsorption studies of nitrobenzene by particulate matter and sediment in the aquatic environment have not been studied comprehensively. Mabey et al. (1981) estimated the sediment sorption coefficient to be 36 based on the K_{ow} value of 74; this value suggests that adsorption may not be significant. The EXAMS computer simulation (Burns et al., 1981) predicts that ≤2% of the nitrobenzene present in rivers and lakes will remain in sediments. The laboratory-scale waste stabilization pond study of Davis et al. (1983) showed that only ~3% of the total amount of nitrobenzene underwent sedimentation in the pond. U.S. EPA (1980c) developed an adsorption isotherm for nitrobenzene using pulverized activated carbon. They fitted the data to the logarithmic form of the Freundeich equation:

$$\text{Log } X/M = \text{Log } K + 1/N \text{ Log } C_f$$

where:

$X = C_o - C_f$ the amount of compound adsorbed from a given volume of solution

M = the weight of activated carbon

C_o = amount of compound in the untreated solution

C_f = the amount of compound remaining in the treated water

For nitrobenzene at a pH of 7.5 they determined the coefficients K and 1/n to be 68 and 0.43, respectively. The relevance of activated carbon adsorption to soil adsorption coefficients is uncertain.

2.1.5.3. **BIOACCUMULATION** -- Freitag et al. (1982) examined the bioaccumulation of nitrobenzene in the golden orfe using a static water test for a period of 3 days; the BCF was found to be <10. Tests using algae (Chlorella fusca) measured the BCF to be 24 (Freitag et al., 1982; Geyer et al., 1984).

Veith et al. (1979) used a flowthrough aquarium and a 28-day exposure to measure a BCF of 15 for nitrobenzene in the fathead minnow.

^{14}C-labeled nitrobenzene was studied for its effect in a model aquatic ecosystem developed by Lu and Metcalf (1975). The ecosystem contained green algae, snails, water fleas, mosquito larvae and fish. The nitrobenzene in the system was resistant to degradation, but it was not stored or ecologically magnified. Aniline, acetanilide, aminophenols and nitrophenols were identified as metabolites of nitrobenzene.

Kawasaki (1980) used the MITI test to determine a BCF in fish of <10. Kenaga (1980) predicted the BCF value for nitrobenzene to be 9 based on its WS. These BCF values indicate that bioaccumulation of nitrobenzene in aquatic organisms is not expected to be significant.

2.1.5.4. **PERSISTENCE** -- The overall persistence of nitrobenzene in river water was estimated to be 0.3-3 days (Zoeteman et al., 1980).

2.2. AIR

Atmospheric chemical removal processes include photolysis and reaction with hydroxyl radicals and ozone. Experimentally derived rate constants for these processes were not located in the available literature as cited in the Appendix. Cupitt (1980) theoretically calculated the rate constant for the

reaction between •OH and nitrobenzene to be 0.06×10^{-12} cm³/molecule-sec; assuming an average atmospheric •OH concentration of 10^6 molecules/cm³, a half-life of ~133 days can be calculated. In moderately polluted atmospheres, the half-life may be more rapid by a factor of 10. The rate constant calculated by Cupitt (1980) for the reaction between nitrobenzene and ozone in the air (5×10^{23} cm³/molecule-sec) suggests no environmental significance for this reaction.

Nojima and Kanno (1977) examined the photolysis of nitrobenzene in air contained in a pyrex glass reaction vessel. The vessel was irradiated for 5 hours with a xenon lamp ($\geq$300 nm); 38% of the nitrobenzene was degraded. o-Nitrophenol and p-nitrophenol were identified as photolysis products; photolysis in the absence of O_2 also produced phenol. This suggests that direct photolysis of nitrobenzene in the atmosphere may be significant. Cupitt (1980) also suggested that photolysis of nitrobenzene may be significant.

Cupitt (1980) additionally predicted that the physical removal processes in the atmosphere [dissolution (rainfall), adsorption to particles, dry deposition] would not be significant with regards to nitrobenzene.

2.3. SOIL

2.3.1. Microbial Degradation. Alexander and Lustigman (1966) tested the degradation of nitrobenzene in a mineral solution inoculated with a suspension of Niagara silt loam soil. The decomposition of the nitrobenzene by the soil microflora required >64 days, which indicated the compound was degradation-resistant. Other studies regarding the microbial degradation of nitrobenzene in soil were not located; however, Zoeteman et al. (1980) observed ~100% removal of nitrobenzene from Rhine River water after passage through a soil bank infiltration system; the authors suggested that the removal was due to microbial processes.

2.3.2. Chemical Degradation. Pertinent data regarding the chemical degradation of nitrobenzene in soil were not located in the available literature as cited in the Appendix.

2.3.3. Photolysis. As noted in Sections 2.1.3. and 2.2., photolysis of nitrobenzene in water and in air may be significant fate processes; this implies that photolysis of nitrobenzene from soil surfaces may occur. Callahan et al. (1979) suggested that nitrobenzene photoreduction on soil humus may be significant, although experimental data are not available.

Freitag et al. (1982) measured the photolysis of nitrobenzene absorbed in silica gel and exposed to UV irradiation of $\geq$290 nm; during 17 hours of exposure, 6.7% of the nitrobenzene was photolyzed to CO_2.

2.3.4. Adsorption/Leaching. Wilson et al. (1981) measured the movement of nitrobenzene through Lincoln fine sand (92% sand, 5.9% silt, 2.1% clay, 0.087% organic content) in a soil column experiment. The nitrobenzene was found to move readily through the soil column, demonstrating significant leaching.

The K_{oc} of an organic compound can be estimated from the WS or K_{ow} by using the following equations:

$$\text{Log } K_{oc} = 3.64\text{-}0.55 \text{ Log WS (in ppm)} \quad \text{(Kenaga and Goring, 1980)} \quad (2\text{-}1)$$

$$\text{Log } K_{oc} = 0.544 \text{ Log } K_{ow} + 1.377 \quad \text{(Kenaga and Goring, 1980)} \quad (2\text{-}2)$$

$$\text{Log } K_{oc} = 0.44\text{-}0.54 \text{ Log WS (in mole fraction)} \quad \text{(Karickhoff et al., 1979)} \quad (2\text{-}3)$$

For nitrobenzene, the K_{oc} values calculated from Equations 2-1, 2-2 and 2-3 are ~70, 250, and 230, respectively. These values indicate a medium to

high mobility in soil. Estimation of K_{oc} from molecular topology and quantitative structure-activity relationship analysis (Sabljic, 1984) yields a K_{oc} value of ~650, indicating a moderate soil mobility.

2.3.5. Volatilization. Jury et al. (1984) predicted volatilization rates for nitrobenzene from an ideal soil by application of a soil screening model which uses physical properties, Henry's Constants and K_{oc} values of an organic compound to estimate its transport fate in soil. In dry soil, nitrobenzene is predicted to have a volatilization half-life of 19 days when placed 10 cm below the soil surface and 1.6 days when placed 1 cm deep.

2.4. SUMMARY

In the aquatic environment, photolysis, volatilization and biodegradation are potentially significant fate processes. The microbial degradation of nitrobenzene has been demonstrated to be significant when using selected wastewaters, activated sludges and sewage as inocula media. The relative importance of microbial degradation in natural water and soil environments is difficult to predict from the available data. It does appear that properly acclimated microorganisms are capable of degrading nitrobenzene. Nitrobenzene is not expected to bioaccumulate significantly in aquatic organisms.

Reaction with hydroxyl radicals and photolysis appear to be the significant fate mechanisms in the ambient atmosphere.

In soil, nitrobenzene appears susceptible to significant leaching, although field studies have not been reported. Nitrobenzene is predicted to evaporate from soils quite rapidly depending upon its depth in the soil.

3. EXPOSURE

3.1. WATER

Nitrobenzene can be released into the aquatic environment through wastewater from its commercial manufacture (Gruber, 1975) and commercial use.

Cole et al. (1984) reported the preliminary findings of the U.S. EPA Nationwide Urban Runoff Program (NURP) that determined the levels of priority pollutants in urban stormwater runoff. Nitrobenzene was not detected in 86 samples analyzed from 15 different United States cities.

Young et al. (1983) detected a mean nitrobenzene level of 20 µg/ℓ in the final effluent from the Los Angeles County Municipal Wastewater Treatment Plant in July, 1978; however, in November of 1980, the level was <10 µg/ℓ. Fielding et al. (1981) detected nitrobenzene (concentration and specific site not reported) in the surface water of an upland reservoir used as a source of drinking water. Nelson and Hites (1980) detected nitrobenzene at a concentration of 8 ppm in soil along the Buffalo River, but did not find it in three river sediment samples.

Piet and Morra (1983) found nitrobenzene at levels of 1-10 µg/ℓ in Rhine River water in the Netherlands, but did not detect it in tap water. Zoeteman et al. (1980) similarly detected nitrobenzene in raw Rhine River water at levels of 0.5 µg/ℓ before bank filtration and <0.01 µg/ℓ after filtration. Average concentrations of 0.1-5.4 µg nitrobenzene/ℓ have been found in water from the Maas and Waal Rivers in the Netherlands (Meijers and Van der Leer, 1976).

Akiyama et al. (1980) identified nitrobenzene in seawater near Japan but did not quantify it. Sugiyama et al. (1978) detected nitrobenzene levels of 0.16-0.99 ppb in Japanese river water and seawater.

The gross analysis available from the U.S. EPA STORET Data Base regarding nitrobenzene is listed in Table 3-1.

TABLE 3-1

Nitrobenzene Concentrations in Water, Sediment and Fish Tissue from U.S. EPA STORET Data Base

Concentration	Water (µg/ℓ) (n=5097)	Sediment[a] (µg/kg) (n=538)	Fish Tissue[b] (µg/kg) (n=255)
Maximum	50,000	200,000	70
Minimum	0	0	0
Mean	103	2,265	2.4

[a]Dry weight

[b]Wet weight

3.2. FOOD

Pertinent data regarding the monitoring of nitrobenzene in foods were not located in the available literature as cited in the Appendix. There have been reports of nitrobenzene poisoning resulting from its contamination of alcoholic drinks (Nabarro, 1948).

3.3. INHALATION

The major atmospheric emission source of nitrobenzene is its production and subsequent use in aniline production (Harkov et al., 1983). Nitrobenzene is also emitted to the atmosphere by evaporation from its use as a solvent (Graedel, 1978). Photochemical reactions in the atmosphere involving benzene or alkylbenzenes may produce nitrobenzene (Katagiri and Ohashi, 1978; Hoshino et al., 1978).

Nitrobenzene has been extensively monitored in the ambient air of New Jersey (Bozzelli and Kebbekus, 1979, 1982; Bozzelli et al., 1980, 1981). Average levels of ~0.5-1.0 ppb were detected in the air of industrialized cities such as Rutherford, Newark, Middlesex and Piscataway. Pellizzari (1978) detected nitrobenzene in the ambient air near the industrial complex in Geismar, LA at levels ranging from not detected to 20 ppb. Pellizzari (1977) monitored for, but did not detect, nitrobenzene in the air of Staten Island, NY. Brodzinsky and Singh (1982) summarized the U.S. monitoring data available until 1980; nitrobenzene was detected (trace amounts or larger) in 104/609 total samples analyzed with a median concentration of less than the detection limit (or ~0.01 ppb).

3.4. DERMAL

Pertinent data regarding the dermal monitoring of nitrobenzene were not located in the available literature as cited in the Appendix.

4. PHARMACOKINETICS

4.1. ABSORPTION

Nitrobenzene can be absorbed by inhalation, cutaneous exposure and ingestion; however, the two more common routes of exposure are reported to be pulmonary and cutaneous exposure (Dorigan and Hushon, 1976; U.S. EPA, 1980b). As reviewed by Beauchamp et al. (1982) and U.S. EPA (1980b), the absorption rate of nitrobenzene during inhalation is 80% (Piotrowski, 1972, 1977; Salmowa et al., 1963). Nitrobenzene, in both vapor and liquid state, can be absorbed through the skin. The U.S. EPA (1980b) reported that according to Piotrowski (1972) the maximal cutaneous absorption of liquid nitrobenzene is 0.2-3.0 mg/cm²/hour, depending on the skin temperature. According to Salmowa et al. (1963) as reviewed by Beauchamp et al. (1982), however, initial percutaneous absorption rates of 0.5-2.5 mg/cm²/hour decreased after several hours to 0.1-0.2 mg/cm²/hour following application to the forearm of 15 mg/cm³ of liquid nitrobenzene. Feldman and Maibach (1970) found that ~1.5% of the radioactivity from a 4 μg/cm² liquid dose of [^{14}C]nitrobenzene applied to the forearm of humans was excreted in the urine in a 24-hour period indicating that at least 1.5% was absorbed. As stated by Beauchamp et al. (1982) the apparent discrepancies in the studies of Feldman and Maibach (1970) and Salmowa et al. (1963) may be due to the differences in the doses. No corrections for evaporation were made in either study.

The absorption of nitrobenzene via the gastrointestinal tract can be inferred from the metabolism and excretion studies of Rickert et al. (1983), Robinson et al. (1951) and Parke (1956) (Sections 4.3. and 4.4.) and from the acute toxicity studies in animals and humans in which ingestion of nitrobenzene results in toxic effects.

4.2. DISTRIBUTION

As reviewed by Dorigan and Hushon (1976), 2 days after the oral administration of 0.25 mℓ of radioactive nitrobenzene to rabbits, ~54% of the administered radioactivity was absorbed by the tissues, accumulating in the fat and intestinal tract (Parke, 1956). Eight days after the oral administration of 0.25 mℓ of radioactive nitrobenzene, ~8% of the administered radioactivity remained in the experimental animals, predominantly in their fat. Because no free nitrobenzene was detected, Parke (1956) concluded that it was the metabolites of nitrobenzene, rather than unchanged nitrobenzene, that remained in the rabbit tissues 8 days after dosing and that were subsequently slowly eliminated in the urine and expired air.

4.3. METABOLISM

As reviewed by Beauchamp et al. (1982), 56% of the administered oral dose of 150-200 mg/kg of nitrobenzene was accounted for in the urine of rabbits within 2 days of dosing (Robinson et al., 1951); the major metabolite was identified as p-aminophenol.

As discussed in Section 4.2., Parke (1956) administered 0.25 mℓ of [^{14}C]nitrobenzene to rabbits by gavage. p-Aminophenol in the urine accounted for 31% of the administered radioactivity within 4 or 5 days after dosing. Smaller amounts of m-aminophenol, o-aminophenol, p-nitrophenol and m-nitrophenol, each comprising 3-9% of the administered radioactivity, were also identified in the urine. Less than 1% of the administered radioactivity was identified as aniline, o-nitrophenol, 4-nitrocatechol, nitroquinol or p-nitrophenylmercapturic acid.

To study the species and strain differences in nitrobenzene metabolism and excretion, three male Fischer 344 rats, three male CD rats and three male B6C3F$_1$ mice were treated with a single oral dose of 225 mg/kg of

[^{14}C]nitrobenzene (Rickert et al., 1983). In addition, three males from each of the two strains of rats were treated with a single oral dose of 22.5 mg/kg of [^{14}C]nitrobenzene (Rickert et al., 1983). As indicated in Table 4-1, p-hydroxyacetanilide, p-aminophenol, p-nitrophenol, m-nitrophenol and their glucuronide and sulfate conjugates and two unidentified metabolites were found in the urine of mice within 72 hours of dosing. The CD rats did not have any p-aminophenol in their urine. The proportion of the various metabolites found in the urine was different in the CD rat as compared with the B6C3F$_1$ mouse, with 21.3-31% of the administered radioactivity being recovered as the unidentified metabolite "I" in CD rats. As in the B6C3F$_1$ mice, the metabolites recovered from the urine of CD rats were found in their unbound state and as conjugated glucuronides and sulfates. The Fischer 344 rats did not have any p-aminophenol or unidentified metabolite "II" in their urine. In addition, no free metabolites or glucuronide-conjugated metabolites were identified in the urine of Fischer 344 rats. The p-hydroxyacetanilide, p-nitrophenol and m-nitrophenol identified in the urine of Fischer 344 rats were recovered only as the respective sulfate conjugates.

Bile collected for 12 hours after the oral administration of 225 mg/kg of [^{14}C]nitrobenzene to three male Fischer 344 and three male CD rats contained six radioactive compounds, three of which were identified as 4-hydroxy-3-methylthioacetanilide, 2-acetamide-3-(5'-acetamido-2'-hydroxy-phenylthio)-propanoic acid and 5-(5'-acetamido-2'-hydroxyphenyl)glutathione (Rickert et al., 1983). When nitrobenzene was administered to germ-free Fischer 344 rats under the same experimental conditions, however, none of the six metabolites found in the bile of normal Fischer 344 rats were identified in the bile of the germ-free Fischer 344 rats. Approximately 1.1% of

TABLE 4-1

Urinary Excretion of Nitrobenzene Metabolites in Rats and Mice Given an Oral Dose of Nitrobenzene[a,b]

Percentage of Dose Excreted as:		Fischer 344 Rats		CD Rats		B6C3F$_1$ Mice
		Dose (mg/kg)				
		225	22.5	225	22.5	225
p-Hydroxyacetanilide	free	0	0	1.3 ± 0.2[c]	0.9 ± 0.2	0.4 ± 0.0[c]
	glucuronide	0	0	1.8 ± 0.6[c]	1.1 ± 0.1[d]	3.1 ± 0.3[c]
	sulfate	19.0 ± 0.9	19.8 ± 2.8	5.8 ± 1.2[c]	1.7 ± 0.9[d]	0.4 ± 0.1[c]
	total	19.0 ± 0.9	19.8 ± 2.8	8.8 ± 1.8[c]	3.7 ± 1.1[d]	3.9 ± 0.4[c]
p-Aminophenol	free	0	0	0	0	0.1 ± 0.1
	glucuronide	0	0	0	0	0.2 ± 0.2
	sulfate	0	0	0	0	9.4 ± 1.3[c]
	total	0	0	0	0	9.7 ± 1.2[c]
p-Nitrophenol	free	0	0	2.2 ± 0.6[c]	0.7 ± 0.2[d]	0.8 ± 0.1[c]
	glucuronide	0	0	0.5 ± 0.1[c]	0.6 ± 0.0[d]	0.1 ± 0.1
	sulfate	19.9 ± 1.1	23.3 ± 2.1	10.3 ± 2.9[c]	5.6 ± 1.8[d]	6.3 ± 1.1[c]
	total	19.9 ± 1.1	23.3 ± 2.1	13.0 ± 2.4	6.9 ± 2.0[d]	7.2 ± 1.2[c]
m-Nitrophenol	free	0	0	1.2 ± 0.4[c]	0.4 ± 0.1[d]	0.1 ± 0.1
	glucuronide	0	0	0.5 ± 0.2[c]	0.5 ± 0.1[d]	0
	sulfate	10.2 ± 0.6	11.6 ± 1.4	6.2 ± 1.7	3.8 ± 1.2[d]	6.1 ± 1.2[c]
	total	10.2 ± 0.6	11.6 ± 1.4	7.9 ± 1.4	4.7 ± 1.4[d]	6.2 ± 1.2[c]
Unidentified metabolite I		9.8 ± 0.7	9.0 ± 0.5	25.3 ± 1.2[c]	31.1 ± 2.1[d]	4.8 ± 0.7[c]
Unidentified metabolite II		0	0	5.7 ± 4.0	16.4 ± 5.6[d]	2.6 ± 0.2[c]

[a]Source: Rickert et al., 1983

[b]Values are x ± SEM for three animals over a 72-hour period.

[c]Significantly different from Fischer 344 rats which had received 225 mg NB/kg (Student's t-test; $p \leq 0.05$)

[d]Significantly different from Fischer 344 rats which had received 22.5 mg NB/kg (Student's t-test; $p \leq 0.05$)

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the administered radioactivity was identified as a single polar metabolite in the bile of germ-free Fischer 344 rats treated with [^{14}C]nitrobenzene (Rickert et al., 1983). After normal male Fischer 344 rats were treated with antibiotics to sterilize the gastrointestinal tract, the amount of urinary p-hydroxyacetanilide and an unidentified metabolite were decreased 94 and 86%, respectively (Levin and Dent, 1982).

Goldstein et al. (1984) confirmed the work of Reddy et al. (1976) who demonstrated that intestinal microflora affect the development of methemoglobinemia after ingestion of nitrobenzene and, in addition, reported that dietary content can alter the metabolism of intestinal microflora thereby affecting the ability of ingested nitrobenzene to produce methemoglobinemia. The reduction of nitrobenzene, an important step in the metabolism of nitrobenzene (Beauchamp et al., 1982; Dorigan and Hushon, 1976), appears to occur in the intestinal tract and to be modulated by the intestinal microflora (Goldstein et al., 1984). *In vitro* studies by Harada and Omura (1980) indicated that nitrobenzene was reduced by rat hepatic microsomal enzymes in the presence of NADPH or NADH under anaerobic conditions. The significance of this to *in vivo* conditions is questionable since generally enough oxygen is available to preclude reduction via P-450.

An abstract of a Polish study (Bomski and Bomska, 1968) reported that iron-deficient rabbits had higher levels of urinary p-aminophenol than normal rabbits after subcutaneous administration of nitrobenzene.

4.4. EXCRETION

The species and strain differences in nitrobenzene metabolism and excretion were studied in three male Fischer 344 rats, three male CD rats and three male B6C3F$_1$ mice treated with a single oral dose of 225 mg/kg of [^{14}C]nitrobenzene (Rickert et al., 1983). In addition, three males from

each of the two strains of rats were treated with a single oral dose of 22.5 mg/kg of [^{14}C]nitrobenzene (Rickert et al., 1983). The urine, feces and expired air were collected at various intervals during a 72-hour period. As indicated in Table 4-2, 60.8±1.1 to 65.8±2.4% of the administered radioactivity was recovered from the urine of both strains of rats within 72 hours of dosing regardless of the dose administered. In mice, however, a significantly lower percentage (34.7±4.8%) of the administered radioactivity was recovered from the urine within 72 hours of dosing. Peak urinary excretion of radioactivity occurred within 6-24 hours of treatment. Rickert et al. (1983) concluded that the slow urinary excretion of nitrobenzene metabolites was due to slow metabolism, rather than slow absorption of nitrobenzene. As indicated on Table 4-1 and discussed more fully in Section 4.3., p-hydroxyacetanilide, p-aminophenol, p-nitrophenol, m-nitrophenol and two unidentified metabolites were observed in the urine of B6C3F$_1$ mice. The same compounds, except for p-aminophenol, were observed in the urine of CD rats. The same compounds, except for p-aminophenol and one of the unidentified metabolites, were observed in the urine of Fischer 344 rats. Although the Fischer 344 rats did not exhibit a dose-dependent excretion of metabolites, the CD rats did. Increasing the dose of nitrobenzene administered to CD rats increased the percentage of dose excreted as p-hydroxyacetanilide, p-nitrophenol and m-nitrophenol and decreased the percentage of dose excreted as unidentified metabolite I and II (Rickert et al., 1983).

Bile collected for 12 hours after the oral administration of 225 mg/kg of [^{14}C]nitrobenzene to three male Fischer 344 and three male CD rats contained 1.8 and 3.8%, respectively, of the administered radioactivity (Rickert et al., 1983). The bile contained six radioactive peaks, three of

TABLE 4-2

Excretion of Radioactivity After Administration of [^{14}C]Nitrobenzene to Rats and Mice[a,b]

Percentage of Dose Excreted in:	Fischer 344 Rat		CD Rat		$B6C3F_1$ Mouse
	225 mg/kg (per os)	22.5 mg/kg (per os)	225 mg/kg (per os)	22.5 mg/kg (per os)	225 mg/kg (per os)
Urine	63.2 ± 2.1	65.8 ± 2.4	60.8 ± 1.1	64.5 ± 0.8	34.7 ± 4.8[c]
Feces	14.2 ± 0.7	21.4 ± 1.8[c]	11.8 ± 1.1	11.5 ± 0.1	18.8 ± 0.4
Expired air	1.6 ± 0.1	1.0 ± 0.6	2.5 ± 0.3	0.8 ± 0.2	0.8 ± 0.1
Total	79.0 ± 2.2	88.2 ± 1.8[c]	75.1 ± 1.1	76.8 ± 1.0	54.3 ± 4.7[c]

[a]Source: Rickert et al., 1983

[b]Values are x ± SEM for three animals over a 72-hour period

[c]Significantly different from Fischer 344 rats given 225 mg/kg NB per os (Student's t-test, $p<0.05$)

which were identified as 4-hydroxy-3-methylthioacetanilide, 2-acetamido-3-(5'-acetamido-2'-hydroxyphenylthio) propanoic acid and 5-(5'-acetamido-2'-hydroxyphenyl) glutathione. Rickert et al. (1983) stated that biliary excretion of radioactivity was not fast enough to account for all of the fecal radioactivity found.

Both p-aminophenol and p-nitrophenol were identified in the urine of humans occupationally exposed to nitrobenzene (Piotrowski, 1977; Ikeda and Kita, 1964). As reviewed by U.S. EPA (1980b), Piotrowski (1977) reported that metabolic transformation and excretion of nitrobenzene was slower (by an order of magnitude) in humans than in rats or rabbits. In humans, urinary p-nitrophenol reaches its highest concentration ~4 days after nitrobenzene exposure and can be used to approximate the level of nitrobenzene exposure. Human urinary metabolites, however, account for 20-30% of the administered dose of nitrobenzene (Piotrowski, 1977). At low levels of nitrobenzene exposure, the chief urinary metabolite in humans was reported to be p-nitrophenol as indicated by an abstract of a Czech study (Kunor et al., 1973).

5. EFFECTS

5.1. CARCINOGENICITY

Although pertinent data regarding the carcinogenicity of nitrobenzene were not located in the available literature as cited in the Appendix, nitro- benzene has been nominated to the National Cancer Institute as a candidate for carcinogen bioassay (Helmes et al., 1982). Nitrobenzene, however, was not included on the most current list of chemicals scheduled for testing by the National Toxicology Program (NTP, 1985). A 2-year inhalation carcino- genicity study in which Fischer 344 and Spraque-Dawley rats are exposed to 0, 1, 5 and 25 ppm (0, 5, 25 and 126 mg/m^3) and B6C3F$_1$ mice are exposed to 0, 5, 25 or 50 ppm (0, 25, 126 or 252 mg/m^3) is currently being conducted by CIIT (1984).

5.2. MUTAGENICITY

As indicated in Table 5-1, nitrobenzene did not increase the frequency of reverse mutations in Salmonella typhimurium strains TA92, TA94, TA98, TA100, TA1535, TA1537, TA1538 either in the presence or absence of metabolic activation when tested by plate incorporation or spot test technique (Garner and Nutman, 1977; Chui et al., 1978; Shimizu et al., 1983; Ho et al., 1981; Haworth et al., 1983; Anderson and Styles, 1978; Miyata et al., 1981). Hughes et al. (1984) reported that nitrobenzene was also negative for reverse mutation in S. typhimurium strains TA97, TA98 or TA100 with and without activation when tested in the vapor phase. Suzuki et al. (1983) tested the mutagenicity of nitrobenzene in the presence of norharman. In the presence of metabolic activation and norharman, 100 µg/plate of nitro- benzene significantly increased the frequency of reverse mutations in S. typhimurium strain TA98, but not in strain TA100. The frequency of reverse mutations was not increased by nitrobenzene in S. typhimurium strains TA98

TABLE 5-1

Mutagenicity of Nitrobenzene

Assay	Indicator Organism	Strain	Concentration/ Dose	Application Method	Activation System	Response	Reference
Reverse mutation	Salmonella typhimurium	TA1538	50 and 100 µg/plate	plate incorporation	+/-	-/-	Garner and Nutman, 1977
Reverse mutation	S. typhimurium	TA98 TA100	0.1, 1 and 10 µmol/disk	spot test	-	-	Chiu et al., 1978
Reverse mutation	S. typhimurium	TA98 TA100 TA1535 TA1537 TA1538	0.08-10.24 µL/plate	plate incorporation	+/-	-/-	Shimizu et al., 1983
Reverse mutation	S. typhimurium	TA98	0.025-0.5 mg/plate	plate incorporation	+	-	Ho et al., 1981
Reverse mutation	S. typhimurium	TA98 TA100 TA1535 TA1573	0.0-1000.0 µg/plate	plate incorporation	+/-	-/-	Haworth et al., 1983
Reverse mutation	S. typhimurium	TA98 TA100 TA1535 TA1538	4.0, 20.0, 100.0, 500.0 and 1000.0 µg/plate	plate incorporation	+	-	Anderson and Styles, 1978
Reverse mutation	S. typhimurium	TA92 TA94 TA98 TA100 TA1535 TA1537	0.03-3 mg/plate	plate incorporation	+/-	-/-	Miyata et al., 1981
Reverse mutation	S. typhimurium	TA97 TA98 TA100	0.0-3333.0 µg/plate	vapor phase	+/-	-/-	Hughes et al., 1984

or TA100, regardless of the presence or absence of metabolic activation when norharman was not included in the bacterial assay. Suzuki et al. (1983) concluded that norharman (found in tobacco smoke) may act as a co-mutagen with nitrobenzene.

In an *in vivo-in vitro* hepatocyte DNA repair assay, male Fischer 344 rats were treated by gavage with 200 or 500 mg/kg of nitrobenzene in corn oil (Mirsalis et al., 1982). Twelve hours after treatment, liver cells from the rats gavaged with nitrobenzene were isolated and unscheduled DNA synthesis was measured by quantitative autoradiography. Nitrobenzene did not cause a significant increase in unscheduled DNA synthesis (Mirsalis et al., 1982).

5.3. TERATOGENICITY

An abstract of a Russian study (Kazanina, 1968) reported that 125 mg/kg/day of nitrobenzene was administered subcutaneously to pregnant rats. The days on which the nitrobenzene was administered were not clearly identified in the abstract, but treatment was reportedly begun on days 4-6 or 9-12 of gestation. Delayed embryogenesis and disorders of organogenesis, as well as an alteration of placental redox processes, were observed. The U.S. EPA (1980b) reported that 4 of the 30 fetuses examined in the Kazanina (1968) study had gross morphological defects.

Additional pertinent data regarding the teratogenicity of nitrobenzene were not located in the available literature as cited in the Appendix.

5.4. OTHER REPRODUCTIVE EFFECTS

In a study by Bond et al. (1981), necrotic primary and secondary spermatocytes, as well as multinucleated giant cells, were observed in the seminiferous tubules between 1 and 4 days after a single oral dose of 300 mg/kg of nitrobenzene to rats. Bond et al. (1981) also reported decreased numbers of spermatocytes in the epididymis within 3 days of treatment.

Additional pertinent data regarding other reproductive effects of nitrobenzene were not located in the available literature as cited in the Appendix.

5.5. CHRONIC AND SUBCHRONIC TOXICITY

Pertinent data regarding the effects of chronic or subchronic oral exposure to nitrobenzene were not located in the available literature as cited in the Appendix.

In a subchronic inhalation study, groups of 10 male and 10 female Fischer 344 rats, Sprague-Dawley CD rats and B6C3F$_1$ mice were exposed to nitrobenzene at concentrations of 0, 5, 16 or 50 ppm (0, 25, 81 or 252 mg/m^3) for 6 hours/day, 5 days/week for 90 days (CIIT, 1984). The animals were evaluated for clinical appearance, body weight changes, clinical chemistry, hematology, urinalyses, organ weights and gross and microscopic pathology. Clinical observations, body weight changes and results of urinalyses were unremarkable. The only treatment-related change in clinical chemistry parameters was a significant ($p \leq 0.05$) and dose-related increase in serum methemoglobin levels in Fischer rats at $\geq$25 mg/m^3, in CD rats at $\geq$81 mg/m^3 and in mice at 252 mg/m^3. Hematologic evidence of increased hematopoiesis and hemolytic anemia, including reticulocytosis, was observed at $\geq$81 mg/m^3 in Fischer rats and at 252 mg/m^3 in CD rats, but not in mice. Histologic evidence of hemolytic anemia and increased hematopoiesis included incidences and severity of hemosiderosis and extramedullary hematopoiesis in the spleens of Fischer and CD rats at $\geq$25 mg/m^3. Increased hemosiderosis also occurred in mice at $\geq$25 mg/m^3. At 25 mg/m^3, these lesions were mild and/or occurred with an incidence similar to that of the respective control groups. Increased spleen weights were observed in rats at $\geq$81 mg/m^3 and in mice at 252 mg/m^3.

Dose-related increased incidences and/or severity of toxic nephrosis were observed in rats, but not mice. At 25 mg/m³, the severity of the nephrosis was described as "minimum or very slight degree." At 252 mg/m³, CD rats had increased kidney weights.

Hepatic lesions were also observed in rats and mice. The incidence of focal centrilobular necrosis was increased in Fischer rats at 252 mg/m³ compared with control. In CD rats, liver lesions included increased incidences of hepatocellular hypertrophy and Kupffer cell pigmentation at ≥25 mg/m³, and increased periportal basophilia and enlarged nucleoli at ≥81 mg/m³. Mice had centrilobular hepatocellular hyperplasia at ≥81 mg/m³.

Rats, but not mice, had testicular effects. All male Fischer rats exposed to 252 mg/m³ had decreased testicular weight and moderate to marked degeneration of the testicular epithelium. This lesion was not observed at lower exposures or in controls. In CD rats, bilateral testicular atrophy was observed in 9/10 males at 252 mg/m³ and 1/9 males at 25 mg/m³. Severe degeneration of the spermatogenic epithelium was observed in 10/10 male CD rats at 252 mg/m³ and 1/10 males at 25 mg/m³. The high dose CD males had a complete lack of mature sperm in the epididymis. A very slight degree of spermatogenic epithelial loss occurred in 2/10 males at 81 mg/m³, but these rats did not have testicular atrophy. Testicular weight was decreased at 252 mg/m³.

Increased incidences and severity of vacuolization of the zona reticularis of the adrenal gland was observed in female mice at ≥25 mg/m³, but the toxicologic significance of this finding is unknown.

Abstracts of two Russian studies (Andreeshcheva, 1970; Khanin, 1969) reported the effects of nitrobenzene inhalation exposure on rats for 98 and

70-82 days, respectively. Rats that were exposed to an unspecified concentration of nitrobenzene developed sulfhemoglobinemia at a greater rate than they developed methemoglobinemia (Andreeshcheva, 1970). Rats that were exposed to 0.06-0.1 mg/m³ of nitrobenzene developed toxicodystrophic encephalopathy of the CNS and inflammation of the internal organs (Khanin, 1969). No other details about the treatment schedules were provided in either abstract.

Neurotoxic and hepatotoxic effects were described in a case report of a woman who had been exposed occupationally to nitrobenzene for 17 months in a paint factory (Ikeda and Kita, 1964). For 2 months, the woman had been exposed to "high concentrations". Effects included headache, nausea, vertigo, parasthesia of the legs, hyperalgesia of the hands and feet, enlarged liver, jaundice and increased retention of bromosulfophthalein.

5.6. OTHER RELEVANT INFORMATION

Table 5-2 summarizes the LD_{50} values for nitrobenzene exposure. Absorbed via inhalation, cutaneous application and ingestion, the primary targets for nitrobenzene are the blood, the nervous system, peripheral metabolism and the skin (Dorigan and Hushon, 1976). As reviewed by Beauchamp et al. (1982), methemoglobinemia has been reported after acute, short-term occupational exposure to nitrobenzene (Chandler, 1919; Hamilton, 1919; Donovan, 1920; Gregory, 1906; Harrison, 1977). Sulfhemoglobinemia (Manu, 1978) and anemia (OSHA, 1978; Dorigan and Hushon, 1976) may also occur after nitrobenzene poisoning. Mice appear to be more resistant to methemoglobin formation than rats, dogs or humans, presumably because they have a higher level of methemoglobin reductase activity (Dorigan and Hushon, 1976). Goldstein and Rickert (1984) have recently shown that the covalently bound ^{14}C concentration in red blood cells of rats was 6-13

TABLE 5-2

Acute Toxicity of Nitrobenzene*

Species	Route	LD_{50} (mg/kg)
Rat	oral	640
Rat	skin	2100
Rat	intraperitoneal	640

*Source: U.S. EPA, 1980b

times greater than that of mice after a single oral dose of 75-300 mg/kg of radioactive nitrobenzene had been administered to each species. The entire reticuloendothelial system may be affected by nitrobenzene exposure, as evidenced by splenic hypertrophy and hyperplasia in rats after subcutaneous administration of 0.7 mℓ/kg/day of nitrobenzene for up to 23 weeks (Yamada, 1958). The effects of nitrobenzene on the nervous system are demonstrated by the development of headache, vertigo, nausea, nystagmus, convulsions and coma, although some of these effects may be secondary to the anoxia caused by methemoglobinemia (Beauchamp et al., 1982; Dorigan and Hushon, 1976).

OSHA (1978) reported that human exposure to vapor concentrations of ≥6 ppm of nitrobenzene resulted in headache, vertigo and small amounts of methemoglobinemia; exposure to vapor concentrations of ≥40 ppm of nitrobenzene resulted in intoxication. In the same summary (OSHA, 1978), the odor threshold for nitrobenzene was reported to be 1.9 ppm. Because of its organoleptic and short-term toxic effects (headache, cyanosis and vertigo), the human exposure data reported in the literature describe acute and/or short-term effects, rather than chronic or subchronic effects of nitrobenzene.

According to the review by Beauchamp et al. (1982), liver changes, including hepatomegaly, have been reported in humans after occupational exposure to nitrobenzene (Ikeda and Kita, 1964) and in rats after administration of subcutaneously injected nitrobenzene for up to 23 weeks (Yamada, 1958). Bond et al. (1981) reported hepatic lesions in rats after a single oral treatment with nitrobenzene. An increase in the activity of liver microsomal enzymes was reported in rats after daily subcutaneous injection

of nitrobenzene for up to 30 days (Wisniewska-Knypl et al., 1975). Pulmonary effects such as edema, emphysema, atelectasis, hypertrophy and adenomatous hyperplasia were reported in rabbits treated with subcutaneous or intravenous administration of nitrobenzene (Yamada, 1958; Matsumara and Yoshida, 1959).

Facchini and Griffiths (1981) reported that the intestinal microflora were important in reducing nitrobenzene to the compound which actively caused methemoglobinemia. Their study confirmed the inability of nitrobenzene to induce methemoglobinemia in antibiotic-treated animals. Biaglow et al. (1977) suggested that the ability of nitrobenzene to sensitize hypoxic cells to radiation may be due to the inhibition of oxygen utilization which is sometimes caused by nitrobenzene. As discussed in Section 5.4., a single oral dose of nitrobenzene disrupted normal spermatogenesis in rats (Bond et al., 1981).

English abstracts of Russian studies reported that subcutaneous administration of 200 mg/kg of nitrobenzene increased serotonin levels in rats treated for 2 months (Kulinskaya, 1974) and caused hyperplasia of the adrenal fascicular zone in guinea pigs treated every other day for 6 months (Makotchenko and Akhmetov, 1972). Subcutaneous administration of nitrobenzene to rats resulted in sulfhemoglobinemia, methemoglobinemia, Heinz body formation and anemia (Vasilenko and Zvezdai, 1972). Yordanova et al. (1971) reported hyperplasia of the "lymphoid reticular" cells, a possible early phase of more severe bone marrow lesions, and impairment of copper and iron metabolizing enzymes. English abstracts of several studies published in Romania had previously reported that nitrobenzene altered iron metabolism (Goldstein and Tarpa, 1970; Goldstein et al., 1970). Vrabiescu et al. (1981) reported that the age at which an animal is exposed to nitrobenzene affects the mortality rate in rats.

6. AQUATIC TOXICITY

6.1. ACUTE TOXICITY

The 24-, 48-, 72- and 96-hour LC_{50} values for the bluegill sunfish, Lepomis macrohirusof were determined to be 135, 105, 64.2 and 42.6 mg/ℓ, respectively (U.S. EPA 1978). Holcombe et al. (1984) reported that flowthrough acute 24-, 48-, 72- and 96-hour LC_{50} values for fathead minnows, Pimephale promolas, were 163, 156, 127 and 117 mg nitrobenzene/ℓ, respectively. During the 96-hour tests, narcosis occurred at 139 mg/ℓ, loss of equilibrium occurred at 75.4 mg/ℓ and lethargy was reported at 52.6 mg/ℓ. LeClerc (1960) reported the 6-hour minimum lethal dose for redbelly dace minnows, Chrosomus sp., was 20-24 mg/ℓ in distilled water and 90-100 mg/ℓ in hard water. The NOEC following 96-hour exposures was 10.0 mg nitrobenzene/ℓ. The 96-hour LC_0, LC_{50} and LC_{100} values determined for zebrafish, Brachydanio rerio, were 60, 112.5 and 170 mg nitrobenzene/ℓ, respectively (Wellens, 1982). Juhnke and Luedemann (1978), each conducting separate lethality tests using the golden orfe, Leuciscus idus melanotus, reported 48-hour LC_0, LC_{50} and LC_{100} values of 48, 60 and 72 mg/ℓ, respectively, (tests by Juhnke) or 48, 89 and 130 mg nitrobenzene/ℓ, respectively, (tests by Luedemann). Tests in the himedaka, Oryzias latipes, were conducted for 48 hours to estimate 24- and 48-hour LC_{50} values of 24.0 and 20.0 mg nitrobenzene/ℓ, respectively (Tonogai et al., 1982).

For the marine sheepshead minnow, Cyprinodon variegatus, the U.S. EPA (1978), Heitmuller et al. (1981) and LeBlanc (1984) all reported that 24-, 48- and 72-hour LC_{50} values were >120 mg nitrobenzene/ℓ. The 96-hour LC_{50} value, however, was 58.6 mg/ℓ and the 96-hour NOEC was 21.7 mg/ℓ (U.S. EPA, 1978; Heitmuller et al. 1981; LeBlanc, 1984).

The freshwater crustacean, Daphnia magna, was tested for sensitivity to nitrobenzene in studies by the U.S. EPA (1978), LeBlanc (1980, 1984) and Bringmann and Kuehn (1982). As reported by U.S. EPA (1978) and LeBlanc (1980, 1984), the 24- and 48-hour LC_{50} values were 24.4 and 27.0 mg/ℓ, respectively. The 48-hour NOEC was 0.46 mg nitrobenzene/ℓ. Bringmann and Kuehn (1982) reported 24-hour EC_0, EC_{50} and EC_{100} values as 26, 50 and 100 mg nitrobenzene/ℓ, respectively.

In the marine shrimp, Mysidopsis bahia, 24-, 48-, 72- and 96-hour LC_{50} values were 6.72-12.0, 5.86, 6.68 and 6.68 mg nitrobenzene/ℓ, respectively (U.S. EPA, 1978; LeBlanc, 1984). The 96-hour NOEC value was <0.36 mg/ℓ, notably lower than the 96-hour LC_{50} value.

6.2. CHRONIC EFFECTS

Toxicity tests by Black et al. (1982) were conducted using embryo-larval stages of rainbow trout, Salmo gairdneri and leopard frogs, Rana pipiens. Embryos were exposed to six levels of nitrobenzene from 30 minutes after fertilization through hatching (23 days for trout; 5 days for frogs) and 4 days post-hatching. Trout were exposed at 0.001, 0.010, 0.12, 0.36, 0.91 and 11.9 mg nitrobenzene/ℓ. At ≥0.36 mg/ℓ, no embryos survived until hatching. Hatching success was 3, 21, and 62% at 0.12, 0.010 and 0.001 mg/ℓ, respectively. The frequency of teratic larvae increased in a dose-related manner; the incidence of teratic larvae was 3, 13 and 33% of hatching larval exposed at 0.001, 0.010 and 0.12 mg nitrobenzene/ℓ, respectively. No change in larval survival was evident during the 4-day post-hatching exposure period. The chronic LC_{50} for embryo-larval stage trout was estimated at 0.002 mg/ℓ.

Embryos and larvae of the frog were exposed to 0.001, 0.010, 0.05, 0.10, 0.41 and 1.27 mg nitrobenzene/ℓ (Black et al., 1982). Hatching success

was not affected at levels <0.10 mg/ℓ but at levels of 0.10, 0.41 and 1.27 mg/ℓ, hatching success was, 90, 81 and 66%, respectively. Survival of tadpoles during the 4-day post-hatching exposure period was reduced in the three highest dose level groups. The chronic LC_{50} for embryos until hatching was >1.27 mg/ℓ while the LC_{50} for exposure until 4 days post-hatching was 0.64 mg nitrobenzene/ℓ.

Kerster and Schaeffer (1983) exposed brine shrimp nauplii, Artemia sabina, to nitrobenzene at 0.25-25 mg/ℓ for 24 hours to determine its teratogenic effect on growth. This teratogenic test was based on the disruptive effect of pollutants on elongation of the nauplii between age 24-48 hours. Nitrobenzene at the levels tested inhibited elongation of the nauplii.

6.3. PLANT EFFECTS

The freshwater algae, Salenastrum capricornutum, was exposed to nitrobenzene at levels as high as 120 mg/ℓ for up to 96 hours (U.S. EPA, 1978). EC_{50} values for growth inhibition were >120, 64, 62.2, and 44.1-42.8 mg/ℓ following 24-, 48-, 72- and 96-hour exposures, respectively. The NOEC for S. capricornutum was 3.86 mg nitrobenzene/ℓ. Bringmann and Kuehn (1978, 1980) determined the toxicity threshold of nitrobenzene for cell multiplication inhibition in a blue-green algae, Microcystis aeruginosa, and a green algae, Scenedesmus quadricauda. Following 8-day incubations the onset of growth inhibition occurred at 1.9 and 33 mg/ℓ in the blue-green and green algae, respectively.

The marine algae, Skeletonema costatum, was exposed to nitrobenzene for up to 96 hours to determine EC_{50} values for growth inhibition (U.S. EPA, 1978). The 24-, 48-, 72- and 96-hour EC_{50} values were 22.0, 13.7, 9.95, and 9.65-10.3 mg/ℓ, respectively. The NOEC was <1.20 mg nitrobenzene/ℓ.

6.4. RESIDUE

Pertinent data regarding the residue of nitrobenzene in aquatic organisms were not located in the available literature as cited in the Appendix. Data regarding the environmental fate of nitrobenzene in water were discussed in Chapter 2.

6.5. OTHER RELEVANT INFORMATION

Bringmann and Kuehn (1980) reported toxicity threshold levels of 7.0 and 1.9 mg nitrobenzene/ℓ for inhibition of cell multiplication in the bacteria, Pseudomonas putida, and the protozoan, Entosiphon sulcatum. Exposures were for 7 days and 72 hours, respectively.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

The American Conference of Governmental Industrial Hygienists (ACGIH, 1983) adopted a TWA-TLV of 5 mg/m³ (1 ppm) for an 8-hour nitrobenzene exposure and a 15-minute STEL of 10 mg/m³ (2 ppm) with a caution that exposure by the cutaneous route includes the mucous membranes and eyes and that exposure can occur by air borne contamination as well as by direct skin contact. The TLV was based on occupational exposures which did not result in the development of headaches, methemoglobinemia or anemia in workers (ACGIH, 1980).

The Occupational Safety and Health Administration (OSHA) has established a standard for nitrobenzene exposure of 5 mg/m³ (1 ppm) (Code of Federal Regulations, 1981).

The ILO/WHO Committee on Occupational Health recommended that 5 mg/m³ be the maximum allowable atmospheric concentration of nitrobenzene in the workplace (Goldstein, 1975)

The U.S. EPA (1980b) suggests a water quality criterion of 30 µg/ℓ based on organoleptic effects.

Based on the TLV, an interim ADI of 4.0 mg/day was reported by the U.S. EPA (1985), above which cyanosis caused by methemoglobinemia was observed in humans. An uncertainty factor of 10 was used.

7.2. AQUATIC

Guidelines and standards for the protection of aquatic organisms from the toxic effects of nitrobenzene were not located in the available literature as cited in the Appendix. The U.S. EPA (1980b) suggested criteria

levels of <27 and 6.68 mg/ℓ for freshwater and marine organisms and noted that sensitive species would show at these levels. Based on the more recent chronic toxicity data in rainbow trout, toxic effects were evident at 0.001 mg/ℓ (Black et al., 1982).

8. RISK ASSESSMENT

Although Helmes et al. (1982) reported that nitrobenzene has been recommended to the National Cancer Institute for testing, no study is being conducted under the auspices of NTP (1985). CIIT (1984) is conducting a 2-year inhalation carcinogenicity study in Fischer 344 and Sprague-Dawley CD rats and in $B6C3F_1$ mice. Nitrobenzene was not mutagenic in S. typhimurium (Garner and Nutman, 1977; Chiu et al., 1978; Shimizu et al., 1983; Ho et al., 1981; Haworth et al., 1983; Anderson and Styles, 1978; Miyata et al., 1981; Hughes et al., 1984) and did not cause unscheduled DNA synthesis in rat hepatocytes (Mirsalis et al., 1982). Nitrobenzene was mutagenic in one strain of S. typhimurium in the presence of norharman and metabolic activation (Suzuki et al., 1983). An abstract of a Russian study (Kazanina, 1968), in which delayed and abnormal embryogenesis was reported, is the only data regarding the teratogenicity of nitrobenzene.

Studies of chronic and subchronic oral exposure of animals to nitrobenzene were not located. CIIT (1984), however, conducted a 90-day inhalation study in which rats and mice were exposed to 0, 5, 16 or 50 ppm (0, 25, 81 or 252 mg/m³) for 6 hours/day, 5 days/week. In rats, dose-related significantly increased levels of methemoglobin, increased incidence and severity of increased hemosiderosis and hematopoiesis in the spleen, toxic nephrosis in the kidneys and liver lesions (increasing in severity from hepatocellular hypertrophy to focal necrosis) were observed. At 25 mg/m³, the incidence of spleen, kidney and liver lesions was similar to control and/or the severity was minimal. At $\geq$81 mg/m³, rats had changes in hematologic parameters indicative of hemolytic anemia and increased spleen and liver weights. At 252 mg/m³, male rats had decreased testicular weight, high

incidences of severe degeneration of the testicular spermatogenic epithelium and bilateral testicular atrophy. One rat at 25 mg/m³ also had severe degeneration; the lesion occurred in 2/20 males at 81 mg/m³, but the severity was minimal. In mice, at 25 mg/m³ increased hemosiderosis in the spleen was observed, which became more severe at higher levels. Increased incidences and severity of vacuolization of the zona reticularis of the adrenal gland were observed in female mice at $\geq$25 mg/m³, but the toxicologic significance is unknown. Mice also had hepatocellular hyperplasia at $\geq$81 mg/m³ and increased weights of liver and spleen and methemoglobinemia at 252 mg/m³.

Pending the results of the 2-year inhalation carcinogenicity study in rats and mice, a tentative ADI can be derived from the 90-day study by CIIT (1984). The exposure level of 25 mg/m³ can be considered a LOAEL in rats and mice.

To calculate the ADI, the inhalation exposures must be converted to equivalent doses in units of mg/kg/day by multiplying the exposure level by 6 hours/24 hours and by 5 days/7 days to convert to continuous exposure, by the inhalation rates of the animals of (0.223 m³/day for rats, 0.039 m³/day for mice), by an absorption factor of 0.8, and by dividing by the weight of the animal (assumed to be 0.35 kg for rats and 0.03 kg for mice). The LOAEL of 25 mg/m³ is, therefore, equivalent to 2.24 mg/kg/day for rats and 4.64 mg/kg/day for mice.

The LOAEL of 4.64 mg/kg/day is divided by an uncertainty factor of 10,000 (10 for interspecies extrapolation, 10 to approximate chronic exposure, 10 to estimate a NOAEL from a LOAEL, and 10 to protect the most sensitive individuals of the human population) to calculate an ADI of 0.00046 mg/kg/day or 0.032 mg/day for a 70 kg man.

The ADI of 0.032 mg/day is ~120 times lower than that which could be derived from the TLV and considers the hepatic, renal and testicular effects of nitrobenzene, as well as methemoglobinemia and hematologic effects. This value should be re-examined when chronic oral data for this compound are available.

9. REPORTABLE QUANTITIES

9.1. REPORTABLE QUANTITY (RQ) RANKING BASED ON CHRONIC TOXICITY

The only available study suitable for RQ derivation was a 90-day inhalation study in rats and mice exposed to 0, 25, 81 and 252 mg/m³, 6 hours/day, 5 days/week (CIIT, 1984). The details of this study were discussed in Section 5.5. Data used to calculate CS values are presented in Table 9-1.

The inhalation exposures were transformed into equivalent animal doses by multiplying by 6 hours/24 hours and 5 day/7 days to convert to continuous exposure, by the animal inhalation rate (0.223 m³/day for rats, 0.039 m³/day for mice) and by dividing by the animal body weight (0.35 kg for rats, 0.03 kg for mice). Absorption was assumed to be 100%. To calculate the MED, the animal dose was multiplied by the cube root of the ratio of the animal body weight to the human body weight (70 kg) and by the human weight to express the MED in units of mg/day. In addition, the dose was divided by an uncertainty factor of 10 to approximate chronic exposure.

At the exposure level of 25 mg/m³, evidence of hemolytic anemia was observed including hemosiderosis in the spleen of rats and increased hematopoiesis in the spleen of rats and mice. These effects became more severe as exposure increased. The MED of 3.1 mg/day calculated from the mouse data is slightly lower than that calculated from the rat data (3.4 mg/day). The RV_d associated with an MED of 3.1 mg/day is 4.8. The effect of hemolytic anemia with compensatory increased hemotopoiesis warrants an RV_e of 5. The CS of 24 is obtained by multiplying the RV_d by the RV_e and is equivalent to an RQ of 100.

TABLE 9-1

Composite Scores for the Toxicity of Nitrobenzene[a]

Route	Species	Exposure	Dose (mg/kg/day)	Chronic Human MED (mg/day)[b]	RV_d	Effect	RV_e	CS	MQ
Inhalation	mouse	25 mg/m³, 6 hours/day, 5 day/week,	5.8	3.1	4.8	Hemolytic anemia with compensatory increased hematopoiesis	5	24	100
Inhalation	rat	81 mg/m³, 6 hours/day, 5 days/week, 90 days	9.2	11.0	3.9	Nephrosis and liver necrosis	6	23.4	100
Inhalation	rat	252 mg/m³, 6 hours/day, 5 days/week, 90 days	28.7	34.3	3.2	Testicular atrophy, degeneration of spermatogenic epithelium, absence of mature sperm in epididymis	8	25.6	100

[a]Source: CIIT, 1984

[b]The dose was divided by an uncertainty factor of 10 to approximate chronic exposure.

At the exposure level of 81 mg/m³, there were increased incidences and severity of toxic nephrosis and liver necrosis in rats. The MED of 11.0 mg/day corresponds to an RV_d of 3.9, the RV_e for histologic evidence of necrosis and nephrosis without apparent decrement of organ function is 6, the CS is 23.4 and the RQ is 100.

At 252 mg/m³, the most severe effect observed was bilateral testicular atrophy accompanied by severe degeneration of the spermatogenic epithelium and complete absence of mature sperm in the epididymis of rats. The MED of 34.3 mg/day corresponds to an RV_d of 3.2, the RV_e associated with decreased reproductive capacity is 8, the CS is 25.6 and the RQ is 100.

Therefore, the CSs calculated for the effects at the three exposure levels are virtually identical and all correspond to an RQ of 100. Since the highest CS was obtained from the data at the highest exposure, these data are recommended as the basis of the RQ for nitrobenzene (Table 9-2).

9.2. WEIGHT OF EVIDENCE AND POTENCY FACTOR ($F=1/ED_{10}$) FOR CARCINOGENICITY

No completed carcinogenicity studies of nitrobenzene were located in the available literature as cited in the Appendix. Helmes et al. (1982), however, have recommended to the Chemical Selection Working Group of the National Cancer Institute that nitrobenzene be considered for testing. The recommendation was based on the moderate suspicion that nitrobenzene is carcinogenic because it is the nitro analog of aniline and because of the substantial potential for human exposure. Aniline hydrochloride was carcinogenic in an NCI bioassay (NCI, 1978). Testing of nitrobenzene, however, is not scheduled by the NTP (1985). A 2-year inhalation carcinogenicity study in which Fischer 344 rats and Sprague-Dawley CD rats are exposed to 5, 25 or 125 mg/m³ and B6C3F_1 mice are exposed to 25, 126 or 252 mg/m³ is being conducted by CIIT (1984).

TABLE 9-2

Nitrobenzene

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	inhalation
Dose*:	34.3 mg/day
Effect:	testicular atrophy, degeneration of spermatogenic epithelium, absence of mature sperm in epididymis
Reference:	CIIT, 1984
RV_d:	3.2
RV_e:	8
Composite Score:	25.6
RQ:	100

*Equivalent human dose

Because the carcinogenicity of nitrobenzene has not as yet been adequately tested in animals or sufficiently evaluated in humans, nitrobenzene cannot be classified as to its carcinogenicity for humans. Therefore, according to IARC methodology, nitrobenzene should be classified as a group 3 chemical, pending the results of the 2-year inhalation study.

10. REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). 1980. Documentation of the Threshold Limit Values, 4th ed. (Includes Supplemental Documentation, 1981, 1982, 1983). Cincinnati, OH. p. 303.

ACGIH (American Conference of Governmental Industrial Hygienists). 1983. Threshold Limit Values for Chemical Substances and Physical Agents in the Workroom Environment with Intended Changes for 1983-1984. Cincinnati, OH. p. 27.

Akiyama, T., M. Koga, R. Shinohara, A. Kido and S. Etoh. 1980. Detection and identification of trace organic substances in the aquatic environment. J. UOEH. 2: 285-300.

Alexander, M. and B.K. Lustigman. 1966. Effect of chemical structure on microbial degradation of substituted benzenes. J. Agric. Food Chem. 14: 410-413.

Anbar, M. and P. Neta. 1967. A compilation of specific bimolecular rate constants for the reactions of hydrated electrons, hydrogen atoms and hydroxyl radicals with inorganic and organic compounds in aqueous solution. Int. J. Appl. Radiat. Isot. 18: 493-523.

Anderson D. and J.A. Styles. 1978. An evaluation of 6 short-term tests for detecting organic chemical carcinogens. Appendix II. The bacterial mutation test. Br. J. Cancer. 37: 924-930.

Andreeshcheva, N.G. 1970. Features and criteria of the toxic action of some nitro and amino benzenes. Gig. Sanit. 35(4): 44-47. (CA 73:23600S)

Banerjee, S., S.H. Yalkowsky and S.C. Valvani. 1980. Water solubility and octanol/water partition coefficients of organics. Limitations of the solubility-partition coefficient correlation. Environ. Sci. Technol. 14(10): 1227-1229.

Barltrop, J.A. and N.J. Bunce. 1968. Organic photochemistry. Part VIII. The photochemical reduction of nitro-compounds. J. Chem. Soc. (12): 1467-1474.

Beauchamp, Jr., R.O., R.D. Irons, D.E. Rickert, D.B. Couch and T.E. Hamm, Jr. 1982. A critical review of the literature on nitrobenzene toxicity. CRC Crit. Rev. Toxicol. 11(1): 33-84.

Blaglow, J.E., B. Jacobson, C.L. Greenstock and J. Raleigh. 1977. Effect of nitrobenzene derivatives on electron transfer in cellular and chemical models. Mol. Pharmacol. 13: 269-282.

Black, J.A., W.J. Birge, W.E. McDonnell, A.G. Westerman, B.A. Ramey and D.M. Bruser. 1982. The aquatic toxicity of organic compounds to embryo-larval stages of fish and amphibians. Research Report No. 133 - Univ. Kentucky, Water Resources Research Inst. p. 21, 46, 54, 57.

Bomski, H. and H. Bomska. 1968. Effect of iron on the metabolism of aromatic nitroamino compounds. Effect of systemic iron on nitrobenzene metabolism. Pol. Tyg. Lek. 23(33): 1232-1234. (CA 70:45803a)

Bond, J.A., J.P. Chism, D.E. Rickert and J.A. Popp. 1981. Induction of hepatic and testicular lesions in Fischer-344 rats by single oral doses of nitrobenzene. Fund. Appl. Toxicol. 1(5): 389-394. (CA 96:156876h)

Bozzelli, J.W. and B.B. Kebbekus. 1979. Analysis of selected volatile organic substances in ambient air. Final Report April-Nov. 1978. N.J. Institute of Technology. p. 80.

Bozzelli, J.W. and B.B. Kebbekus. 1982. A study of some aromatic and halocarbon vapors in the ambient atmoshphere of New Jersey. J. Environ. Sci. Health. 17: 693-713.

Bozzelli, J.W., B.B. Kebbekus and A. Greenburg. 1980. Analysis of selected toxic and carcinogenic substances in ambient air in New Jersey. N.J. Institute of Technology.

Bozzelli, J.W., J. Kemp, L. Horgan and B.B. Kebbekus. 1981. Analysis of ambient air at New Jersey locations for selected volatile organic compounds. Proc. 74th Ann. Meet. Air Pollut. Control Assoc. Philadelphia PA. 20 p.

Bringmann, G. and R. Kuehn. 1978. Testing of substances for their toxicity threshold: Model organisms Microcystis (Diplocystis) aeruginosa and Scenedesmus quadricauda. Mitt. Int. Ver. Theor. Angew. Limnol. 21: 275-284.

Bringmann, G. and R. Kuehn. 1980. Comparison of the toxicity thresholds of water pollutants to bacteria, algae, and protozoa in the cell multiplication inhibition test. Water Res. 14(3): 231-241.

Bringmann, G. and R. Kuehn. 1982. Results of toxic action of water pollutants on Daphnia magna Straus tested by an improved standardized procedure. Z. Wasser Abwasser Forsch. 15(1): 1-6. (Ger).

Brodzinsky, R. and H.B. Singh. 1982. Volatile organic chemicals in the atmosphere: An assessment of available data. Atmospheric Science Center. SRI International, Menlo Park, CA. p. 198.

Buccafusco, R.J., S.J. Ells and G.A. LeBlanc. 1981. Acute toxicity of priority pollutants to bluegill (Lepomis macrochirus). Bull. Environ. Contam. Toxicol. 26(4): 446-452.

Burns, L.H., D.M. Cline and R.R. Lassiter. 1981. Exposure Analysis Modeling System (EXAMS). Prepared by Environmental Research Lab., Office of Research and Development, U.S. EPA, Athens, Georgia.

Callahan, M.A., M.W. Slimak, N.W. Gabel, et al. 1979. Water-related Environmental Fate of 129 Priority Pollutants. Volume II. U.S. EPA, Washington, DC. EPA-440/4-79-029B.

Chambers, C.W., H.H. Tabak and P.W. Kabler. 1963. Degradation of aromatic compounds by phenol-adapted bacteria. J. Water Pollut. Control Fed. 35:(12) 1517-1528.

Chandler, W.L. 1919. Physiological action of nitrobenzene vapor on animals. N.Y. Agric. Exp. Stn., Cornell Univ. Memoir. 20: 407. (Cited in U.S. EPA, 1980b; Beauchamp et al., 1982)

Chiu, C.W., L.H. Lee, C.Y. Wang and G.T. Bryan. 1978. Mutagenicity of some commercially available nitro compounds for Salmonella typhimurium. Mutat. Res. 58(1): 11-22.

Chou, W.L., R.H. Speece and R.H. Siddiqi. 1979. Acclimation and degradation of petrochemical wastewater components by M ethane fermentation. Biotechnol. Bioeng. Symp. 8: 391-414.

CIIT (Chemical Industry Institute of Toxicology). 1984. Ninety-day inhalation study of nitrobenzene in F-344 rats, CD rats and B6C3F$_1$ mice with cover letter dated 6/24/84 and EPA response dated 8/06/84. Unpublished study. FYI-OTS-0784-0333 and computer print-out of pathology finding.

CMR (Chemical Marketing Reporter). 1984. Chemical Profile - Nitrobenzene. Chemical Marketing Reporter, July 30, 1984.

Code of Federal Regulations. 1981. OSHA Safety and Health Standards. 29 CFR 1910.1000.

Cole, R.H., R.E. Frederick, R.P. Healy and R.G. Rolan. 1984. Preliminary finds of the priority pollutant monitoring project of the nationwide urban runoff program. J. Water Pollut. Control Fed. 56:(7) 898-908.

Cupitt, L.T. 1980. Fate of toxic and hazardous materials in the air environment. U.S. EPA, Research Triangle Park, NC. EPA-600/3-80-084. NTIS PB80-221948.

Davis, E.M., H.E. Murray, J.G. Liehr and E.L. Powers. 1981. Basic microbial degradation rates and chemical byproducts of selected organic compounds. Water Res. 15(9): 1125-1127.

Davis, E.M., J.E. Turley, D.M. Casserly and R.K. Guthrie. 1983. Partitioning of Selected Organic Pollutants in Aquatic Ecosystems, T.A. Orley and S. Barry, Ed. Pap. Int. Biodeterior. Symp., 5th, Meeting Date 1981, John Wiley and Sons, Inc., UK. p. 176-184.

Donovan, W.M. 1920. The toxicity of nitrobenzene with report of a fatal case. J. Am. Med. Assoc. 74: 1647. (Cited in Beauchamp et al., 1982)

Dorfman, L.M. and G.E. Adams. 1973. Reactivity of the hydroxyl radical in aqueous solution. National Bureau of Standards, Washington, DC. NTIS COM-73-50623. p. 51.

Dorigan J. and J. Hushon. 1976. Air pollution assessment of nitrobenzene. NTIS PB-257-776. p. 96.

Draper, W.M. and D.G. Crosby. 1984. Solar photooxidation of pesticides in dilute hydrogen peroxide. J. Agric. Food Chem. 32: 231-237.

Dunlap, K.L. 1981. Nitrobenzene and nitrotoluenes. In: Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed., Vol. 15, M. Grayson and D. Eckroth, Ed. John Wiley and Sons, Inc., New York. p. 916-925.

Facchini, V. and L.A. Griffiths. 1981. The involvement of the gastrointestinal microflora in nitro-compound-induced methaemoglobinaemia in rats and its relationship to nitrogroup reduction. Biochem. Pharmacol. 30(9): 931-935.

Feldman, R.J. and H.I. Maiback. 1970. Absorption of some organic compounds through the skin in man. J. Invest. Dermatol. 54(5): 399. (Cited in Beauchamp et al., 1982)

Fielding, M., T.M. Gibson, H.A. James, K. McLoughlin and C.P. Steel. 1981. Organic micropollutants in drinking water. Tech. Rep. TR 159 - Water Res. Cent. (Medmenham, England). 47 p.

Freitag, D., H. Geyer, A. Kraus, et al. 1982. Ecotoxicological profile analysis. VII. Screening chemicals for their environmental behavior by comparative evaluation. Ecotoxicol. Environ. Saf. 6(1): 60-81.

Garner, R. and C.A. Nutman. 1977. Testing of some azo dyes and their reduction products for mutagenicity using Salmonella typhimurium TA1538. Mutat. Res. 44: 9-19.

Geyer, H., G. Politzki and D. Freitag. 1984. Prediction of ecotoxicological behaviour of chemicals: Relationship between n-octanol/water partition coefficient and bioaccumulation of organic chemicals by alga Chlorella. Chemosphere. 13(2): 269-284.

Goldstein, I. 1975. Studies on MAC values of nitro and amino derivatives of aromatic hydrocarbons. Adverse Eff. Environ. Chem. Psychotropic Drugs. 1: 153. (Cited in U.S. EPA, 1980b)

Goldstein, R.S. and D.E. Rickert. 1984. Macromolecular covalent binding of [^{14}C]nitrobenzene in the erythrocyte and spleen of rats and mice. Chem. Biol. Interact. 50(1): 27-37.

Goldstein, I. and G. Tarpa. 1970. Repartition of iron-59 in experimental poisoning with nitrobenzene. Med. Lav. 61(4): 237-242. [CA 73(21):107713u)

Goldstein, I., G. Tarpa and S. Berejan. 1970. Metabolism of iron-59 in experimental poisoning with nitrobenzene. Med. Lav. 61(4): 232-236. [CA 73(21):107714v]

Goldstein, R.S., J.P. Chism, J.M. Sherrill and T.E. Hamm, Jr. 1984. Influence of dietary pectin on intestinal microfloral metabolism and toxicity of nitrobenzene. Toxicol. Appl. Pharmacol. 75(3): 547-553.

Gomolka, B. and E. Gomolka. 1983. Degradation of benzene derivatives in aerated municipal wastewaters. Arch. Ochr. Srodowiska. (3-4): 113-123. (CA 101:27741h)

Graedel, T.E. 1978. Chemical Compounds in the Atmosphere. Academic Press, New York, NY. p. 296-297.

Gregory, C.H. 1906. Notes on another case of poisoning or nitrobenzol. Lancet. 1: 1242. (Cited in Beauchamp et al., 1982)

Gruber, G.I. 1975. Assessment of industrial hazardous waste practices, organic chemicals, pesticides and explosives industries. EPA Contract 68-01-2919. NTIS PB 251 307.

Hallas, L.E. and M. Alexander. 1983. Microbial transformation of nitro-aromatic compounds in sewage effluent. Appl. Environ. Microbiol. 45(4): 1234-1241.

Hamilton, A. 1919. Industrial poisoning by compounds of the aromatic series. J. Ind. Hyg. 1: 200. (Cited in Beauchamp et al., 1982)

Hansch, C. and A.J. Leo. 1979. Substituent Constants for Correlation Analysis in Chemistry and Biology. John Wiley & Sons, Inc., New York, NY. p. 339.

Harada, N. and T. Omura. 1980. Participation of cytochrome P-450 in the reduction of nitro compounds by rat liver microsomes. J. Biochem. (Tokyo). 87(5): 1539-1554.

Harkov, R., B. Kebbekus, J.W. Bozzelli and P.J. Lioy. 1983. Measurement of selected volatile organic compounds at three locations in New Jersey during the summer season. J. Air Pollut. Control Assoc. 33(12): 1177-1183.

Harrison, M.R. 1977. Toxic methemoglobinemia-case of acute nitrobenzene and aniline poisoning treated by exchange-transfusion. Anaesthesia. 32(3): 270. (Cited in Beauchamp et al., 1982)

Hawley, G.G. 1977. The Condensed Chemical Dictionary, 9th ed. Van Nostrand Reinhold Co., NY. p. 614.

Haworth, S., T. Lawlor, K. Martelmans, W. Speck and E. Zeiger. 1983. Salmonella Mutagenicity test results for 250 chemicals. Environ. Mutagen. Suppl. 1: 3-142.

Heitmuller, P.T., T.A. Hollister and P.R. Parrish. 1981. Acute toxicity of 54 industrial chemicals to sheepshead minnows (Cyprinodon variegatus). Bull. Environ. Contam. Toxicol. 27(5): 596-604.

Helmes, C.T., V.A. Fung, B. Lewin, K.E. McCaleb, S. Malko and A.M. Pawlovich. 1982. A study of aromatic nitro compounds for the selection of candidates for carcinogen bioassay. J. Environ. Sci. Health, Part A. A17(1): 75-128.

Heukelekian, H. and M.C. Rand. 1955. Biochemical oxygen demand of pure organic compounds. J. Water Pollut. Control Assoc. 29: 1040-1053.

Hine, J. and P.K. Mookerjee. 1975. The intrinsic hydrophilic character of organic compounds. Correlations in terms of structural contributions. J. Org. Chem. 40:(3) 292-298.

Ho, C.H., B.R. Clark, M.R. Guerin, B.D. Barkenbus, T.K. Rao and J.L. Epler. 1981. Analytical and biological analyses of test materials from the synthetic fuel technologies. IV. Studies of chemical structure-mutagenic activity relationships of aromatic nitrogen compounds relevant to synfuels. Mutat. Res. 85(5): 335-345.

Holcombe, G.W., G.L. Phipps, M.L. Knuth and T. Felhaber. 1984. The acute toxicity of selected substituted phenols, benzenes and benzoic acid esters to fathead minnows (Pimephales promelas). Environ. Pollut. (Ser. A). 35(4): 367-381.

Hoshino, M., H. Akimoto and M. Okuda. 1978. Photochemical oxidation of benzene, toluene and ethylbenzene initiated by OH radicals in the gas phase. Kokuritsu Kogai Kenkyusho Kenkyu Hokoku. 5: 43-59. (CA 91:180583c)

Hughes, T.J., C. Sparacino and S. Frazier. 1984. Validation of chemical and biological techniques for evaluation of vapors in ambient air/mutagenicity testing of twelve (12) vapor-phase compounds. EPA-600/1-84-005. NTIS PB84-164219. p. 204.

Ikeda, M. and A. Kita. 1964. Excretion of p-nitrophenol and p-aminophenol in the urine of a patient exposed to nitrobenzene. Br. J. Ind. Med. 21: 210. (Cited in U.S. EPA, 1980b; and Beauchamp et al., 1982)

Johnson, L.D. and J.C. Young. 1983. Inhibition of anaerobic digestion by organic priority pollutants. J. Water Pollut. Control Fed. 55(12): 1441-1449.

Juhnke, I. and D. Luedemann. 1978. Results of the study of 200 chemical compounds on acute fish toxicity using the Golden Orfe test. Z. Wasser Abwasser Forsch. 11(5): 161-164. (Ger).

Jury, W.A., W.F. Spencer and W.J. Farmer. 1984. Behavior assessment model for trace organics in soil: III. Application of screening model. J. Environ. Qual. 13: 573-579.

Karickhoff, S.W., D.S. Brown and T.A. Scott. 1979. Sorption of hydrophobic pollutants on natural sediments. Water Res. 13: 241-248.

Katagiri, Y. and T. Ohashi. 1978. Studies on photochemical air pollution. Formation of nitro-compounds by photochemical reaction of benzene-nitrogen oxides system. Kanagawa-ken Kogai Senta Nempo. 10: 61-64. (CA 93:155036k)

Kawasaki, M. 1980. Experiences with the test scheme under the chemical control law of Japan: An approach to structure-activity correlations. Ecotoxic. Environ. Saf. 4: 444-454.

Kazanina, S.S. 1968. The morphology and histochemistry of hemochorial placentas of rats after nitrobenzene intoxication of the mother. Byull. Eksp. Biol. Med. 65(6): 93-96. [CA 69(17):65819t]

Kenaga, E.E. 1980. Predicted bioconcentration factors and soil sorption coefficients of pesticides and other chemicals. Ecotoxicol. Environ. Saf. 4: 26-38.

Kenaga, E.E. and C.A.I. Goring. 1980. Relationship Between Water Solubility, Soil-Sorption, Octanol-Water Partitioning, and Bioconcentration of Chemicals in Biota. Aquatic Toxicology. ASTMSTP 707. J.G. Gaton, P.R. Parrish and A.C. Hendricks, Ed. American Society for Testing and Materials. p. 78-115.

Kerster, H.W. and D.J. Schaeffer. 1983. Brine shrimp (Artemia salina) nauplii as a teratogen test system. Ecotoxicol. Environ. Saf. 7(3): 342-349.

Khanin, A.G. 1969. Pathohistological changes in the central nervous system and viscera of experimental animals after chronic continous inhalation of toxic substances. Tr. Tsent. Inst. Usoversh. Vrachei. 135: 97-106. [CA 74(1):2341]

Kincannon, D.F., E.L. Stover, V. Nichols and D. Medley. 1983. Removal mechanisms for toxic priority pollutants. J. Water Pollut. Control Fed. 55(2): 157-163.

Kitano, M. 1978. Biodegradability and bioaccumulation test on chemical substances. OECD Tokyo Meeting. Reference Book. TSU-NO: 3.

Kobayashi, H. and B.E. Rittmann. 1982. Microbial removal of hazardous organic compounds. Environ. Sci. Technol. 16: 170A-183A.

Korte, F. and W. Klein. 1982. Degradation of benzene in the environment. Ecotoxicol. Environ. Saf. 6: 311-327.

Kulinskaya, I.L. 1974. Changes in serotonin content and excretion in rats poisoned with nitrobenzene. Narusheniya Metab. Tr. Nauchn. Konf. Med. Inst. Zapadn. Sib. 1: 31-34. [CA 84(19):131035x]

Kunor, V., M. Kuzelova and A. Popler. 1973. Studies of excretion of p-nitrophenol and p-aminophenol in urine of workers in production of nitrobenzene. Prac. Lek. 25(6): 234-238. (CA 86:77800u)

LeBlanc, G.A. 1980. Acute toxicity of priority pollutants to water flea (Daphnia magna). Bull. Environ. Contam. Toxicol. 24(5): 684-691.

LeBlanc, G.A. 1984. Interspecies relationships in acute toxicity of chemicals to aquatic organisms. Environ. Toxicol. Chem. 3(1): 47-60.

LeClerc, E. 1960. The self-purification of streams and the relationship between chemical and biological tests. Proc. 2nd Symp. on the Treatment of Waste Waters. Pergamon Press, London. p. 281. (Cited in McKee and Wolf, 1963)

Leermakers, P.A., H.T. Thomas, L.D. Weis and F.C. James. 1966. Spectra and photochemistry of molecules adsorbed on silica gel. IV. J. Am. Chem. Soc. 88(22): 5075-5083.

Levin, A.A. and J.G. Dent. 1982. Comparison of the metabolism of nitrobenzene by hepatic microsomes and cecal microflora from Fischer-344 rats in vitro and the relative importance of each in vivo. Drug Metab. Disp. 10(5): 450-454.

Lu, P.-Y and R.L. Metcalf. 1975. Environmental fate and biodegradability of benzene derivatives as studied in a model aquatic ecosystem. Environ. Health Perspect. 10: 269-284.

Lutin, P.A., J.J. Cibulka and G.W. Malaney. 1965. Oxidation of selected carcinogenic compounds by activated sludge. Eng. Ext. Ser. (Purdue Univ.). 118: 131-145.

Lyman, W.J., W.F. Reehe and D.H. Rosenblatt. 1982. Handbook of Chemical Property Estimation Methods. Environmental Behavior of Organic Compounds. McGraw-Hill Book Co., New York, NY. p. 960.

Mabey, W.R., J.H. Smith, R.T. Podoll, et al. 1981. Aquatic Fate Process Data for Organic Priority Pollutants. U.S. EPA, Washington, DC. EPA 440/4-81-014.

Makotchenko, V.M. and Zh.B. Akhmetov. 1972. Adrenal cortex function in chronic nitrobenzene poisoning of guinea pigs and the effect of hydrocortisone on the course of poisoning. Farmakol. Toksikol. (Moscow). 35(2): 247-249. [CA 77(3):15182z]

Malaney, G.W. 1960. Oxidative abilities of aniline-acclimated activated sludge. J. Water Pollut. Control Fed. 32: 1300-1311.

Malaney, G.W. and R.E. McKinney. 1966. Oxidative abilities of benzene-acclimated activated sludge. Water Sewage Works. 113: 302-309.

Manu, P. 1978. Early detection of health disturbance in occupational exposure to various risk factors in industry on the basis of changes occurring in various systems or organs. Rev. Ig. Bacteriol. Virusol. Parazitol. Epidemiol. Pneumoftizel Ig. 27(3): 261. (Cited in Beauchamp et al., 1982)

Marion, C.V. and G.W. Malaney. 1964. Ability of activated sludge microorganisms to oxidize aromatic organic compounds. Proc. 18th Ind. Waste Conf., Eng. Bull. Purdue Univ., England Ext. Ser. p. 297-308.

Matsumara. H. and T. Yoshida. 1959. Experimental studies of nitrobenzol poisoning. Kyushu L. Med. Sci. 10: 259. (Cited in Beauchamp et al., 1982)

McCormick, N.G., F.E. Feeherry and H.S. Levinson. 1976. Microbial transformation of 2,4,6-trinitrotoluene and other nitroaromatic compounds. Appl. Environ. Microbiol. 31: 949-958.

McKee, J.E. and H.W. Wolf. 1963. Water Quality Criteria, 2nd ed. Prepared for the Resources Agency of California, State Water Quality Control Board Publ. No. 3-A.

Meijers, A.P. and R.C. van der Leer. 1976. The occurrence of organic micropollutants in the river Rhine and the river Maas in 1974. Water Res. 10(7): 597-604.

Mirsalis, J.C., C.K. Tyson and B.E. Butterworth. 1982. Detection of genotoxic carcinogens in the in vivo-in vitro hepatocyte DNA repair assay. Environ. Mutagen. 4(5): 553-562.

Miyata, R., T. Mohmi, K. Yoshikawa and M. Ishidate, Jr. 1981. Metabolic activation of p-nitrotoluene and trichloroethylene by rat liver S9 or mouse liver S9 fractions in Salmonella typhimurium strains. Eisei Shikensho Hokoku. 99: 60-65. (CA 96:117264m)

Moore, F.W. 1949. The utilization of pyridine by microorganisms. J. Gen. Microb. 3: 143-147.

Nabarro, J.D.N. 1948. A case of acute mononitrobenzene poisoning. Br. Med. J. 1: 929. (Cited in U.S. EPA, 1980a)

NCI (National Cancer Institute). 1978. Bioassay of Aniline Hydrochloride for Possible carcinogenicity. NCI Carcinogenesis Tech. Rep. Ser. No. 130. Also published as DHEW (NIH) 78-1399.

Neely, W.B. 1976. Predicting the flux of organics across the air/water interface. Proc. 3rd Natl. Conf. on Control of Hazardous Material Spills. p. 197-200.

Nei, N., T. Enatsu and G. Terui. 1973. Microbiological decomposition of phenols. IV. Oxidation of aromatic compounds by phenol-utilizing yeasts. Hakko Kogaku Zasshi. 51: 1-11.

Nelson, C.R. and R.A. Hites. 1980. Aromatic amines in and near the Buffalo River. Environ. Sci. Technol. 14: 1147-1149.

Nojima, K. and S. Kanno. 1977. Studies on photochemistry of aromatic hydrocarbons IV. Mechanism of formation of nitrophenols by the photochemical reaction of benzene and toluene with nitrogen oxides in air. Chemosphere. 6: 371-376.

NTP (National Toxicology Program). 1985. Management Status Report Dated 4/08/85.

OSHA (Occupational Safety and Health Administration). 1978. Occupational Health Guideline for Nitrobenzene. U.S. DHHS, PHS, CDC, NIOSH.

Parke, D.V. 1956. Detoxication. LXVIII. The metabolism of C14-nitrobenzene in the rabbit and guinea pig. Biochem. J. 62(2): 339-346. (Cited in Dorigan and Hushon, 1976; Beauchamp et al., 1982)

Pellizzari, E.D. 1977. The measurement of carcinogenic vapors in ambient atmospheres. U.S. EPA, Gulf Breeze, FL. EPA-660/7-77-055.

Pellizzari, E.D. 1978. Quantification of chlorinated hydrocarbons in previously collected air samples. U.S. EPA, Office of Air Quality Planning and Standards. EPA-450/3-78-112. NTIS PB 289804. Research Triangle Park, NC.

Piet, G.J. and C.F. Morra. 1983. Behavior of organic micropollutants during underground passage. In: Artificial Groundwater Recharge (Water Resources Engineering Series), L. Huisman and T.N. Olsthorn Ed. Pitman Publ. p. 336, p. 31-42.

Piotrowski, J.K. 1972. Certain problems of exposure tests for aromatic compounds. Pracov. Lek. 24(2-3): 94. (Cited in Beauchamp et al., 1982)

Piotrowski, J. 1977. Exposure tests for organic compounds in industrial toxicology. U.S. DHEW. NIOSH 77-144. (Cited in U.S. EPA, 1980b)

Pitter, P. 1976. Determination of biological degradability of organic substances. Water Res. 10(3): 231-235.

Reddy, B.G., I.R. Pohl and G. Krishna. 1976. The requirement of the gut flora in nitrobenzene-induced methemoglobinemia in rats. Biochem. Pharmacol. 25: 1119-1122. (Cited in Goldstein et al., 1984)

Rickert, D.E., J.A. Bond, R.M. Long and J.P. Chism. 1983. Metabolism and excretion of nitrobenzene by rats and mice. Toxicol. Appl. Pharmacol. 67(2): 206-214.

Robinson, D., J.N. Smith and R.T. Williams. 1951. Studies in detoxication. 40. The metabolism of nitrobenzene in the rabbit, o-, m- and p-nitrophenols, o-, m- and p-aminophenols and 4-nitrocatechol as metabolites of nitrobenzene. Biochem. J. 50: 228. (Cited in Beauchamp et al., 1982)

Sabljic, A. 1984. Predictions of the nature and strength of soil sorption of organic pollutants by molecular topology. J. Agric. Food Chem. 32: 243-246.

Salmowa, J., J. Piotrowski and U. Neuhorn. 1963. Evaluation of exposure to nitrobenzene. Br. J. Ind. Med. 10: 41. (Cited in Beauchamp et al., 1982; U.S. EPA, 1980b)

Sasaki, S. 1978. The scientific aspects of the chemical substance control law in Japan. In: Aquatic Pollutants: Transformation and Biological Effects, O. Hutzinger, L.H. Letyoeld and B.C.J. Zoeteman, Ed. Pergamon Press, Oxford. p. 283-298.

Shimizu, M., Y. Yasui and N. Matsumoto. 1983. Structural specificity of aromatic compounds with special reference to mutagenic activity in Salmonella typhimurium--a series of chloro- or fluoro-nitrobenzene derivatives. Mutat Res. 116: 217-238.

Smith, R.V. and J.P. Rosazza. 1974. Microbial models of mammalian metabolism. Aromatic hydroxylation. Arch. Biochem. Biophys. 161: 551-558.

SRI (Stanford Research Institute) International. 1984. 1984 Directory of Chemical Producers: United States of America. SRI International, Menlo Park, CA. p. 742.

Stover, E.L. and D.F. Kincannon. 1983. Biological treatability of specific organic compounds found in chemical industry wastewaters. J. Water Pollut. Control Fed. 55: 97-109.

Sugiyama, H., K. Tanaka, K. Fukaya, N. Nishiyama and Y. Wada. 1978. Environmental pollution by chemical substances. II. Determination of aromatic nitro compounds in river and sea water. Eisei Kagaku. 24: 11-18. (CA 89: 152242f)

Suzuki, J., T. Koyama and S. Suzuki. 1983. Mutagenicities of mononitrobenzene derivatives in the presence of norharman. Mutat. Res. 120(2-3): 105-110.

Tabak, H.H., C.W. Chambers and P.W. Kabler. 1964. Microbial metabolism of aromatic compounds. I. Decomposition of phenolic compounds and aromatic hydrocarbons by phenol-adapted bacteria. J. Bacteriol. 87: 910-919.

Tabak, H.H., S.A. Quave, C.I. Mashni and E.F. Barth. 1981. Biodegradability studies with organic priority pollutant compounds. J. Water Pollut. Control Fed. 53(10): 1503-1518.

Tonogai, Y., S. Ogawa, Y. Ito and M. Iwaida. 1982. Actual survey on TLm (median tolerance limit) values of environmental pollutants, especially on amines, nitriles, aromatic nitrogen compounds and artificial dyes. J. Toxicol. Sci. 7(3): 193-203.

U.S. EPA. 1977. Chemical Hazard Information Profile. Nitrobenzene. Office of Toxic Substances, Office of Pesticides and Toxic Substances. Draft.

U.S. EPA. 1978. In-Depth Studies on Health and Environmental Imports of Selected Water Pollutants. Prepared by EG&G Bionomics under contract no. 68-01-4646 for U.S. EPA, Washington, DC.

U.S. EPA. 1980a. Nitrobenzene. Health and Environmental Effects. Washington, DC.

U.S. EPA. 1980b. Ambient Water Quality Criteria for Nitrobenzene. Environmental Criteria and Assessment Office, Cincinnati, OH. EPA 440/4-80-061. NTIS PB 81-117723.

U.S. EPA. 1980c. Carbon adsorption isotherms for toxic organics. Municipal Environmental Research Lab. Cincinnati, OH. EPA-600/8-80-023

U.S. EPA. 1985. Summary of Current Acceptable Daily Intakes (ADIs) for Oral Exposure. Internal Review Draft, ECAO-CIN-432, March, 1985. Environmental Criteria and Assessment Office, Cincinnati, OH.

USITC (U.S. International Trade Commission). 1982. Synthetic Organic Chemicals. U.S. Production and Sales, 1981. USITC Publ. 1292, Washington, DC.

USITC (U.S. International Trade Commission). 1983. Synthetic Organic Chemicals. U.S. Production and Sales, 1982. USITC Publ. 1422, Washington, DC.

USITC (U.S. International Trade Commission). 1984. Synthetic Organic Chemicals. U.S. Production and Sales, 1983. USITC Publ. 1588, Washington, DC.

Vasilenko, N.M. and V.I. Zvezdai. 1972. Comparative evaluation of blood changes in acute and subacute poisoning with aromatic nitro and amino compounds. Farmakol. Toksikol. (Moscow). 35(1): 108-110. [CA 76(21):122529m]

Veith, G.D., D.L. DeFoe and B.V. Bergstedt. 1979. Measuring and estimating the bioconcentration factor of chemicals in fish. J. Fish Res. Board Can. 36: 1040-1048.

Verschueren, K. 1983. Handbook of Environmental Data on Organic Chemicals, 2nd ed. Van Nostrand Reinhold Co., New York. p. 910-912.

Vrabiescu, N.S.A., V.I. Gusic, M. Paunescu and E. Rapeanu. 1981. Studies on poisoning dynamics of nitrobenzene as a function of age. Morphopathological aspects and tanathogenesis. Part II. An. Univ. Bucuresti, Biol. 30: 117-122. [CA 96(23):194614d]

Wellens, H. 1982. Comparison of the sensitivity of Brachydanio rerio and Leuciscus idus by testing the fish toxicity of fish of chemicals and wastewaters. Z. Wasser Abwasser Forsch. 15(2): 49-52.

Wilson, J.T., C.G. Enfield, W.J. Dunlap, R.L. Cosby, D.A. Foster and L.B. Baskin. 1981. Transport and fate of selected organic pollutants in a sandy soil. J. Environ. Qual. 10(4): 501-506.

Wisniewska-Knypl, J.M., J.K. Jablonska and J.K. Piotrowski. 1975. Effect of repeated exposure to aniline, nitrobenzene, and benzene on liver microsomal metabolism in the rat. Br. J. Ind. Med. 32(1): 42-48.

Yamada, Y. 1958. Studies on experimental chronic poisoning with nitrobenzene. Kobe J. Med. Sci. 4: 227. (Cited in Beauchamp et al., 1982; U.S. EPA, 1980b)

Yordanova E., K. Perfanov, P. Uzunov and L. Slivkova. 1971. Hematological changes caused by chronic nitrobenzene exposure. SCR SCI Med. Ann. Sci. Pap. 9(2): 69-77. (Rus.) (Cited in U.S. EPA, 1980b)

Young, D.R., R.W. Gossett, R.B. Baird, D.A. Brown, P.A. Taylor and M.J. Mille. 1983. Wastewater inputs and marine bioaccumulation of priority pollutant organics off southern California. Water Chlorination: Environ. Impact Health Eff. 4(2): 871-884.

Zepp, R.G. and P.F. Schlotzhauer. 1983. Influence of algae on photolysis rates of chemicals in water. Environ. Sci. Technol. 17(8): 462-468.

Zoeteman, B.C.J., K. Harmsen, J.B.H.J. Linders, C.F.H. Morra and W. Slooff. 1980. Persistent organic pollutants in river water and groundwater of the Netherlands. Chemosphere. 9(4): 231-249.

APPENDIX

LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of the following:

CA SEARCH (Files 308, 309, 310, 311, 320)
TOXLINE
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP

These searches were conducted in December, 1984 with the exception of the TOXLINE, which was searched in February, 1984 and was kindly supplied by Dynamac Corp. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7), and the following secondary sources were reviewed:

ACGIH (American Conference of Governmental Industrial Hygienists). 1980. Documentation of the Threshold Limit Values, 4th ed. (Includes Supplemental Documentation, 1981, 1982, 1983). Cincinnati, OH. 486 p.

ACGIH (American Conference of Governmental Industrial Hygienists). 1983. TLVs: Threshold Limit Values for Chemical Substances and Physical Agents in the Workroom Environment with Intended Changes for 1983-1984. Cincinnati, OH. 94 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2A. John Wiley and Sons, NY. 2878 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2B. John Wiley and Sons, NY. p. 2879-3816.

Clayton, G.D. and F.E. Clayton, Ed. 1982. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2C. John Wiley and Sons, NY. p. 3817-5112.

Grayson, M. and D. Eckroth, Ed. 1978-1983. Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed. John Wiley and Sons, NY. 23 Volumes.

Hamilton, A. and H.L. Hardy. 1974. Industrial Toxicology, 3rd ed. Publishing Sciences Group, Inc., MA. 575 p.

IARC (International Agency for Research on Cancer). IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans. WHO, IARC, Lyons, France.

ITII (International Technology Information Institute). 1982. Toxic and Hazardous Industrial Chemicals Safety Manual for Handling and Disposal with Toxicity and Hazard Data. ITII, Tokyo, Japan. 700 p.

NTP (National Toxicology Program). 1984. Toxicology Research and Testing Program. Chemicals on Standard Protocol. Management Status.

Ouellette, R.P. and J.A. King. 1977. Chemical Week Pesticide Register. McGraw-Hill Book Co., NY.

Sax, I.N. 1979. Dangerous Properties of Industrial Materials, 5th ed. Van Nostrand Reinhold Co., NY.

SRI (Stanford Research Institute). 1984. Directory of Chemical Producers. Menlo Park, CA.

U.S. EPA. 1982. Chemical Activities Status Report, 3rd ed. (EPACASR). Office of Pesticides and Toxic Substances, Washington, DC. EPA 560/TIIS-82-002b.

U.S. EPA. 1983. Status Report on Rebuttable Presumption Against Registration (RPAR) or Special Review Process. Registration Standards and the Data Call in Programs. Office of Pesticide Programs, Washington, DC.

U.S. EPA. 1984. CSB Existing Chemical Assessment Tracking System. Name and CAS Number Ordered Indexes. Office of Toxic Substances, Washington, DC.

USITC (U.S. International Trade Commission). 1983. Synthetic Organic Chemicals. U.S. Production and Sales, 1982, USITC Publ. 1422. Washington, DC.

Verschueren, K. 1983. Handbook of Environmental Data on Organic Chemicals, 2nd ed. Van Nostrand Reinhold Co., NY.

Worthing, C.R. and S.B. Walker, Ed. 1983. The Pesticide Manual. British Crop Protection Council. 695 p.

In addition, approximately 30 compendia of aquatic toxicity data were reviewed, including the following:

Battelle's Columbus Laboratories. 1971. Water Quality Criteria Data Book. Volume 3. Effects of Chemicals on Aquatic Life. Selected Data from the Literature through 1968. Prepared for the U.S. EPA under contract No. 68-01-0007. Washington, DC.

Johnson, W.W. and M.T. Finley. 1980. Handbook of Acute Toxicity of Chemicals to Fish and Aquatic Invertebrates. Summaries of Toxicity Tests Conducted at Columbia National Fisheries Research Laboratory. 1965-1978. U.S. Dept. Interior, Fish and Wildlife Serv. Resource Publ. 137. Washington, DC.

McKee, J.E. and H.W. Wolf. 1963. Water Quality Criteria, 2nd ed. Prepared for the Resources Agency of California. State Water Quality Control Board. Publ. No. 3-A.

Pimental, D. 1971. Ecological Effects of Pesticides on Non-Target Species. PB-269605. Prepared for the U.S. EPA, Washington, DC.

Schneider, B.A. 1979. Toxicology Handbook. Mammalian and Aquatic Data. Book 1: Toxicology Data. Office Pesticide Programs, U.S. EPA, Washington, DC. EPA 540/9-79-003. NTIS PB 80-196876.

In addition, the following documents were obtained and reviewed:

U.S. EPA. 1977. Chemical Hazard Information Profile Draft Report, Nitrobenzene, CHIP equivalent: ITC Dossier.

U.S. EPA. 1978. Initial Report of the TSCA Interagency Testing Committee to the Administrator. EPA 560-10-78/001.